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A SEQUENTIAL, MULTIPLE ASSIGNMENT RANDOMIZED TRIAL (SMART) FOR NON-SPECIALIST TREATMENT OF COMMON MENTAL DISORDERS IN KENYA: LEVERAGING THE DEPRESSION AND PRIMARY-CARE PARTNERSHIP FOR EFFECTIVENESS-IMPLEMENTATION RESEARCH (DAPPER) PROJECT (SMART-DAPPER)

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ABSTRACT

Introduction:

Dominated by depression, mental disorders are a leading cause of global disability. Most of the disease burden is in Low and Middle Income Countries (LMICs), where 75% of adults with mental disorders have no service access. Despite nearly 15 years of efficacy studies showing that local non-specialists can provide evidence-based care for depression in LMICs, few studies have advanced to implementation research. As emphasized by a recent World Health Organization (WHO) initiative, integration of depression treatment into existing systems of care is critical to achieving public health impact. Kenyan leaders recently launched an initiative to scale-up treatment for mental disorders in primary healthcare, prioritizing depression. Yet, they lack an evidence base for the two essential treatments – psychotherapy and second-generation antidepressants - without which the scale-up will fall short of its potential. The proposed research responds to this need and builds on our current work in Kisumu, showing that Interpersonal Psychotherapy (IPT) can be delivered by trained non-specialists with high efficacy for the treatment of depression and/or PTSD using fluoxetine or Interpersonal therapy. In the context of the ongoing COVID-19 pandemic, and to adequately respond to and provide additional care for new or worsening mental health needs, we will integrate a phone based screening, assessment and treatment options. Additionally, the study applies a SMART design to manage non-responsiveness to the given treatment by switching or combination.

Objectives: We propose to partner with local and national mental health stakeholders in Kenya to evaluate: (1) non-specialist delivery of evidence-based depression and/or PTSD treatment integrated within existing healthcare centers and by telephone in regard to clinical effectiveness and implementation parameters; including (2) costs and cost-benefit ratios for depression and/or PTSD care. Given that evidence-based psychotherapy and second-generation antidepressants are the two leading first-line treatments for depression and/or PTSD and are feasible to deliver in Kenya, our goal is to test an implementation strategy for improving equitable access to these treatments by integrating them with primary care.

Methodology:

Given the novelty of non-specialist depression care and primary care integration for Kenya, we will use an effectiveness-implementation hybrid design type I, which emphasizes effectiveness outcomes for the new setting and study population, while also gathering implementation data for future scale up. In collaboration with the 80-member FACES team currently providing integrated HIV care to Kisumu County Hospital (KCH) primary care outpatient clinics (~10,000 patients/month), we will randomize 2000 adult KCH and other Kisumu County Ministry of Health primary care patients with Major Depressive Disorder (MDD) to receive IPT delivered in person or by telephone by non-specialists trained in the study or fluoxetine delivered by fluoxetine trained providers in the study and follow them for 30 months. We will use the Exploration, Preparation, Implementation and Sustainment (EPIS) framework to inform the research and incorporate positive findings into practice. Given the high prevalence of MDD-PTSD co- morbidity, we will leverage the R01 to support a Sequential, Multiple Assignment Randomized Trial (SMART) by recruiting an additional 710 participants with MDD and/or PTSD (irrespective of HIV status) for a

total of 2710 participants. Local non-specialists will be trained in mental health care for the SMART and hired through the Kenyan Ministry of Health to work at KCH and other Kisumu County Ministry of Health facilities. After the study, Kisumu County will continue their payroll and the fluoxetine supply.

Data analysis: the study will compare short and long term (relapse) outcomes for IPT versus fluoxetine treatment (Aim 1), and calculate costs and cost-benefit ratios for each treatment arm (Aim 2).

Results:

The results of the proposed research will (1) produce a scalable strategy for delivering depression treatments in sub-Saharan Africa using non-specialists integrated within existing primary care structures and (2) offer policy makers short and long-term cost-benefit options for integrated depression care with corresponding effectiveness and implementation values.

TABLE OF CONTENTS

ABBREVIATIONS AND ACRONYMS

AUDIT: alcohol use disorder identification test
ASQ: Ask Suicide-Screening Questions
BDI: Beck Depression Inventory
CAG: Community Advisory Groups
CTS: Conflict Tactics Scale
CHW/CHV: Community Health Worker/ Community Health Volunteer
DAP: Dynamic Adaptation Process
DAPPER: Depression And Primary-Care Partnership For Effectiveness-Implementation Research
DAS: Dyadic Adjustment Scale
DAST: Drug Abuse Screening Test
DM: Diabetes Mellitus DSM-V: Diagnostic and Statistical Manual of Mental Disorders-V
EPIS: Exploration, Preparation, Implementation and Sustainment
FACES: Family Aids Care and Education Services
GBD: Global Burden of Disease
HIC: High Income Countries
HIV: Human Immune Deficiency Virus
HSE: Baseline Household Socio-Economic Survey
HTN: Hypertension
IPT: Interpersonal Therapy
KCH: Kisumu County Hospital
KEMRI: Kenya Medical Research Institute
KNH: Kenyatta National Hospital
LMIC: Low and Middle Income Countries
MDQ: Mood Disorder Questionnaire
MDSPSS: Multi-dimensional Scale of Perceived Social Support
MDD: Major Depressive Disorder
MINI: Mini International Neuropsychiatric Interview
NACOSTI: National Commission for Science, Technology and Innovation
NIMH: National Institute of Mental Health
PCL: Posttraumatic Stress Checklist
PHQ-2: Patient Health Questionnaire-2
PPB: Pharmacy & Poisons Board
PTSD: Post traumatic stress disorder
RDoC: Research Domain criteria
REDCap: Research Electronic Data Capture
SAM: Self-Assessment Manikin
SMART: Sequential, Multiple Assignment Randomized Trial
THQ: Trauma History Questionnaire
UCSF: University of California, San Francisco
UoN: University of Nairobi

WB: World Bank
WHO: World Health Organisation
WHODAS: World Health Disability Assessment Schedule

OPERATIONAL DEFINITIONS

Interpersonal therapy: a form of psychotherapy (talking treatment) in which the health provider works with the patient to improve interpersonal and intrapersonal communication skills within relationships and to develop social support network

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

Study explanation

Consent

Consent to Participate in a Research Study
Consent to Participant in a Research Study: In-Depth Interview Assessments of Interventions
Consent to Participant in a Research Study: Focus Group Assessment of Implementation
Consent to Participant in a Research Study: In-Depth Interview Assessments of Implementation
Consent for in-depth Assessment Of Implementation Luo

Questionnaires

Alcohol Use Disorders Identification Test (AUDIT)
Ask Suicide-Screening Questions (ASQ)
Beck Depression Inventory (BDI)
Conflicts Tactics Scale-2 (CTS-2)
Drug Abuse Screening Test (DAST)
Dyadic Adjustment Scale (DAS)
HSE: Baseline Household Socio-Economic Survey
Mini International Interview (MINI)
Trauma History Questionnaire (THQ)
Posttraumatic Checklist (PCL)
Mood Disorder Questionnaire (MDQ)
Multi-dimensional Scale of Perceived Social Support (MSPSS)
Self-Assessment Manikin (SAM)
World Health Organization Disability Assessment Schedule (WHODAS)
Patient Health Questionnaire-2 (PHQ-2)
Healthcare utilization, Income and Employment, Education and School Fees, and Time Allocation (SEARCH)
Demographic Health Survey (DHS) – selected questions
Affordability and Access for Treatment
Demographics
Concomitant Medications
Health Co-morbidities

INTRODUCTION

Background

Led by depression, untreated mental disorders are the largest global cause of disability.(Christopher J L Murray et al., 2015),(Ferrari et al., 2013),(Thornicroft et al., 2016) Most of this burden is in Low and Middle Income Countries (LMICs), where 75% of adults with mental disorders have no access to treatment.(Organization, 2008) Despite 15 years of efficacy research demonstrating that evidence-based, low-cost depression treatments can be successfully delivered by non-specialist personnel in low resource settings,(Hyman, 2014),(Vikram Patel et al., 2013),(van Ginneken et al., 2013) morbidity from mental disorders continues to escalate.(Bloom et al., 2011),(Kassebaum et al., 2016),(Shidhaye, Lund, & Chisholm, 2015),(Chisholm et al., 2016) It is vital that global mental health treatment researchers now focus on implementation science to inform scale-up of evidence-based depression care to lower mental health burden. As emphasized by a recent World Health Organization (WHO) initiative,("WHO | Framework on Integrated People-Centred Health Services," n.d.) integration of depression treatment into existing systems of care is critical to achieving public health impact. With high prevalence of Major Depressive Disorder (MDD) in Kenyan primary care populations (26.3%,(Aillon et al., 2014) 3-5 times higher than in the U.S.(Katon, 2003)), treatment for depression is a top concern for Kenya mental health leaders. Knowledge gaps in Kenyan mental health care implementation thwart current scale up efforts. Kenyan mental health leaders recently launched a government-funded initiative to scale-up treatment for mental disorders in primary healthcare, prioritizing

depression.(Bukusi, 2015) Yet, they lack an evidence base to guide programs for the two essential treatments –psychotherapy and second generation antidepressants(Gelenberg et al., 2010)—without which Kenyan care scale-up will fall short of its potential.(Kiima, 2015),(Ndetei et al., 2009) The proposed research responds to this need.

Implementation research on depression treatment within existing LMIC health care systems must consider not only individual treatment benefits in culturally distinct populations, but also barriers affecting access to care, healthcare system capacities, and budget.(Cabassa & Baumann, 2013) Hence, we propose to partner with local and national mental health stakeholders in Kenya to evaluate: (1) non-specialist delivery of evidence-based depression treatment integrated within existing healthcare centers in regards to clinical effectiveness and healthcare system implementation parameters; including (2) costs and cost-benefit ratios for depression care. In collaboration with Family Aids Care and Education Services (FACES), we are already conducting an effectiveness-implementation hybrid type I study (Curran, Bauer, Mittman, Pyne, & Stetler, 2012) (n=300) of Interpersonal Psychotherapy (IPT) delivered by non-specialists for HIV-positive women with co-morbid MDD and posttraumatic stress disorder (Onu et al., 2016),(Meffert, Neylan, Chambers, & Verdeli, 2016). In preliminary analyses, IPT delivered by non-specialists achieves remission in 38% of participants–similar to U.S. effectiveness studies with specialists (36.8%) (Rush et al., 2006) Given that evidence-based psychotherapy and second-generation antidepressants are now considered the two leading first-line treatments for depression(Gelenberg et al., 2010) and are feasible to deliver in Kenya, our goal is to test an implementation strategy for improving equitable access to these treatments by integrating them with primary care. We will leverage

research suggesting that antidepressants and psychotherapy have equivalent short-term results for depression, and that psychotherapy better protects against relapse (long-term result).(Schneier et al., 2012),(Lee et al., 2016),(Hien et al., 2015) We propose an effectiveness-implementation hybrid design type III (Curran et al., 2012) (Depression And Primary-care Partnership for Effectiveness-implementation Research [DAPPER]) to determine the outcomes of non-specialist delivered Interpersonal Psychotherapy (IPT) compared to fluoxetine, including assessment of the service delivery mechanism in regards to availability to attend required treatment schedule and affordability.(Obrist et al., 2007),(Penchansky & Thomas, 1981),(Khanassov et al., 2016),(Levesque, Harris, & Russell, 2013)

Preliminary studies

We are currently conducting an effectiveness-implementation hybrid type I study of depression treatment delivered by non-specialists, integrated with HIV care services at a government primary healthcare center (n=300). We have used individual IPT delivered by non-specialist personnel for MDD and Posttraumatic Stress Disorder (PTSD) in three LMICs, including Darfur refugees in Cairo,(Jiang et al., 2014) Sichuan earthquake survivors (absolute risk reduction of greater than 50% and effect sizes of 2.37 (p=0.018) and 1.94 (p=0.056) for MDD and PTSD, respectively)(Jiang et al., 2014) and our current NIMH-funded randomized, controlled effectiveness-implementation hybrid type I trial of IPT for HIV+ women affected by gender based violence integrated within the FACES-supported Kisumu County primary care clinic at Lumumba health center (enrolment complete [n=300], study ongoing).(Zunner et al., 2015),(Onu, Ongeri, Rota, Atewa, & Meffert, n.d.)

In our current study:

- Clinical outcome domains include mental health (MDD and PTSD diagnostic and symptom measures), HIV (viral load and self-reported anti-retroviral adherence), intimate partner violence, interpersonal functioning, disability, quality of life and neurocognition.
- Implementation and economic domains include human resources for integrating mental health care within the HIV clinic (implementation officer, peer supervision, clinic staff advisory team), treatment protocol adherence (a random 20% of IPT sessions are externally reviewed for IPT adherence), repeated stakeholder engagement (local and national) and a detailed economics core assessing patient-level benefits, formal and informal productivity gains and overall returns on mental health care investment.

In preliminary analyses of post-treatment data (n=194) in the current study in Kisumu, Kenya, non-specialist delivered IPT achieves MDD remission in 38% and PTSD remission in 52% of participants – greater than treatment as usual and higher than U.S. effectiveness studies (30%) with physician-delivered depression care. In a subsample with HIV viral load data (n=116), we have a nearly significant effect (p=0.09) on un-detectability of HIV viral load (clinical goal): 82% of those in IPT have undetectable viral loads after their 12-week treatment, versus only 68% of those in usual care, despite the fact that all participants received usual HIV care, throughout.

Expertise and experience in training nurses in East Africa to administer fluoxetine for depression:

Our team has experience with training nurses and clinical officers to integrate with existing healthcare systems and successfully prescribe fluoxetine for depression, including HIV clinics in a neighbouring region of Uganda. In preliminary analyses of Dr. Akena and Wagner's INDEPTH study (n=415), 66% (n=272) completed a 9 month course of antidepressant therapy. Only 15% (n=61) had prematurely discontinued treatment —a higher rate of adherence than with SSRIs in High Income Countries (HICs). 78% of completers were in full remission at treatment conclusion and 66% in the intent to treat analysis, which classified those who prematurely discontinued treatment as non-responders. The majority of the treatment gains were achieved early in treatment (weeks 6-12), with a 68.5% average reduction on the Patient Health Question 9 item (PHQ-9) from baseline and little further gain with additional treatment.

Hypothesis and Specific Aims:

Aim 1:

Determine the effectiveness of non-specialist-delivered Interpersonal Psychotherapy (IPT), fluoxetine, or combination for MDD and PTSD.

Hypothesis 1a: Initial randomization to IPT or fluoxetine will have similar efficacy for post-treatment remission.

Hypothesis 1b: Participants who remit with IPT or combination treatment will have fewer relapses over follow-up than those who remit with fluoxetine.

Aim 2:

Investigate key presumed mediators of the relationship between treatment and remission

Hypothesis 2a: For initial treatment with IPT, change in social support will mediate the relationship between treatment and remission—improved social support will be associated with remission

Hypothesis 2b: For initial treatment with fluoxetine, change in emotional reactivity will mediate the relationship between treatment and remission—decreased emotional reactivity will be associated with remission.

Aim 3: Identify demographic and clinical moderators of the relationship between treatment and remission.

Hypothesis 3a: Time or cost for transport between participants' residences and KCH, and other Kisumu County Ministry of Health facilities will moderate the relationship between treatment and remission—higher time/cost will decrease the effect of initial treatment with IPT relative to fluoxetine (more treatment visits required for IPT versus fluoxetine treatment).

Hypothesis 3b: Severity of MDD and/or PTSD symptoms among non-remitters will moderate the relationship between subsequent treatment and remission, such that higher severity will decrease the effect of treatment on remission for treatment switch relative to treatment combination.

Hypothesis 3c: Q learning will produce personalized treatment algorithms using the above or other moderators.

Aim 4. Estimate the costs and cost-benefit ratios for fluoxetine and IPT treatment of depression and PTSD.

Hypothesis 4a: Pooled cost-benefit ratios will show that depression and/or PTSD treatment leads to net economic gain for individuals and households at month 6;

Hypothesis 4b: Separate analyses will find that IPT has a more favorable cost-benefit than fluoxetine at month 30.

Aim 5. Determine the acceptability and feasibility of delivering SMART-DAPPER treatments by telephone.

Hypothesis 5a. Telephone IPT will be acceptable and feasible.

Hypothesis 5b. Telephone fluoxetine provider appointments will be acceptable and feasible.

Aim 6. Determine the effect of telephone treatment delivery on retention in care.

Hypothesis 6a. Participants who elect to receive telephone treatment will have higher retention in care than those who receive face-to-face care.

Significance

The results of the proposed research will be significant in two ways:

(1) They will produce a scalable strategy for delivering evidence-based depression treatments in sub-Saharan Africa using non-specialists integrated within existing primary care structures and

(2) They will produce a practical, policy maker "menu" of short and long-term cost-benefit options for integrated depression care with corresponding effectiveness and implementation values.

LITERATURE REVIEW

Depression is now the leading cause of disability in eastern sub-Saharan Africa(Thornicroft et al., 2016),("Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013," 2015) and among the top 5 diseases driving the overall increase of global morbidity and disability.(Christopher J L Murray et al., 2015),(C.J.L. Murray & Lopez, 1996) The 1996 global burden of disease (GBD) report by World Health Organization (WHO) and the World Bank (WB) was the first to put mental disorders on the list of highly disabling conditions.(C.J.L. Murray & Lopez, 1996) Twenty years later, the global disability attributed to mental disorders has increased by 45%.

Depression is higher in primary care populations compared with general populations. In primary care populations of high income countries, 29% of adult outpatients have major depressive disorder, compared with approximately 6.7% of the general population.(Roca et al., 2009),("NIMH » Major Depression Among Adults," n.d.) Preliminary data from

our studies in Kenya indicates an even heavier burden among primary care patients in Kenya, with approximately 50% meeting criteria for major depressive disorder, compared approximately 2.6-5.6% of the general population—a 10-19 fold difference.(Ongeri et al., n.d.)·(Jenkins, Othieno, Ongeri, Sifuna, et al., 2015)·(Hanlon et al., 2014)

Integration of depression treatment with primary care is beneficial to patients and healthcare systems. For more than ten years, it has been established that integrating depression treatment with primary care services produces better results for patients in both the short term and the long term (5 years).(Gilbody, Bower, Fletcher, Richards, & Sutton, 2006)More recent studies have shown that integrated depression care effectively improves depression symptoms, adherence and response to treatment, remission of symptoms, quality of life, function and satisfaction with care.(Thota et al., 2012) Integrated depression care has been shown to be cost-effective.(Jacob et al., 2012) Integrated depression care in LMICs has been advocated for many years, and a completed large scale treatment study in an LMIC shows positive results.(Vikram Patel et al., 2016) In sub-Saharan Africa, numerous studies show that adequate resources for integration of depression and primary care services exist,(Hanlon, Wondimagegn, & Alem, 2010)·(Mugisha et al., 2017)·(V. Patel et al., 2016) with some of the clearest findings in Kisumu County (below).

Integration of depression treatment with primary care is feasible and acceptable at Kisumu County Hospital (KCH) and other Kisumu County Ministry of Health facilities. Kisumu County is one of the more advanced regions of Kenya for research on integration of mental health and primary health care. Our team has shown that interventions to

improve mental health care for primary care outpatients are feasible,(Jenkins, Othieno, Okeyo, Kaseje, et al., 2013) and acceptable to patients(Jenkins, Othieno, Ongeri, Ogutu, et al., 2015) as well as primary health care providers.(Jenkins, Othieno, Okeyo, Aruwa, et al., 2013) Integration of depression care with adult medical outpatient clinics at KCH and other Kisumu County Ministry of Health facilities or over the telephone will benefit from our collaboration with FACES, which currently has large teams at KCH and other Kisumu County Ministry of Health facilities, integrated with the primary care clinics to provide HIV services and ready to partner with this study to facilitate its integration. Furthermore, both local and national mental health policy leaders, as well as the directors of KCH and other Kisumu County Ministry of Health facilities are highly enthused about integration of depression treatment with primary care clinics at KCH and other Kisumu County Ministry of Health facilities given its high prevalence in the region and the burden that untreated depression places on regional primary care systems.

In light of the COVID-19 pandemic, Kenya has appropriately responded with strict stay-home and curfew orders to limit transmission. Yet, these restrictions are likely to worsen symptoms for those already living with Major Depressive Disorder (MDD) and Posttraumatic Stress Disorder (PTSD), the focus of SMART-DAPPER treatment. In order to adapt to the community's mental health care implementation needs, participants will have the option to have their treatment visits (Interpersonal Psychotherapy [IPT] and fluoxetine initiation and management) and assessment visits by telephone.

Prior to randomization, participants will chose if they would prefer to receive their treatment at the health facility in person or by telephone. Participants who are randomized to fluoxetine will collect their medication at the health facility. If

participants do not collect their medication at the health facility, fluoxetine may be delivered to participants in the community.

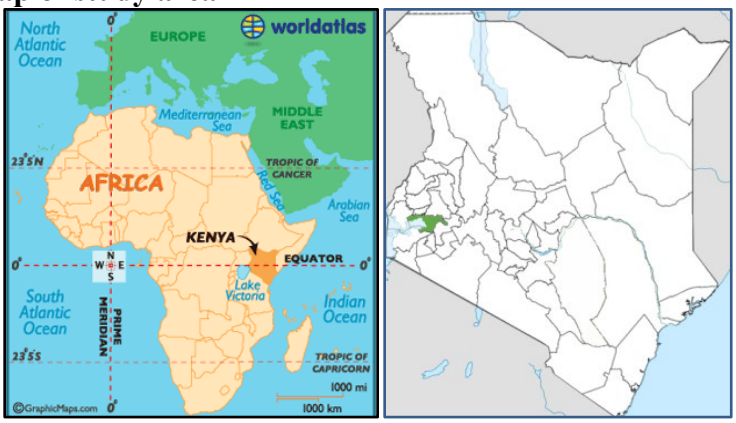
RESEARCH METHODOLOGY AND PROCEDURES

Study location:

Kisumu County is in western Kenya near Lake Victoria and the county capital is Kisumu, the third largest city in Kenya. With its high prevalence of HIV, the region has been a focus of national and international healthcare efforts, with robust research infrastructure (Figure 1).

Kisumu County Hospital is a county government run facility situated at the centre of Kisumu city, just next to Kisumu Bus Park. The facility still hosts the only county psychiatric ward, which serves the whole former Nyanza region. The outpatient department is headed by a physician, 2 Medical Officers, 3 Clinical Officers and Nurses. On estimate 10,000 adult primary care outpatients are seen per month.

Figure 1: Map of study area



Kisumu County Hospital (KCH):
10,000 adult primary care outpatients seen per month

Study Design:

Effectiveness-implementation study designs are a transformative tool for making evidence-based depression care disorders equitably available in LMICs. Recently, Curran

and colleagues defined effectiveness-implementation hybrid study designs.(Curran et al., 2012) These designs include both effectiveness and implementation outcomes, allowing for the collection of data on individual clinical outcomes as well as system-level data on provider training, supervision, financing and workflow in real-world settings. Effectiveness-implementation hybrid designs are a key advancement for global mental health implementation research because they allow monitoring of clinical outcomes with culturally diverse populations, while advancing research to support mental health care scale up.(Meffert et al., 2016) Our team has shown that effectiveness-implementation study designs are feasible in Kisumu County.(Meffert et al., n.d.; Onu et al., 2016) See details in preliminary data, below.

Effectiveness-implementation hybrid designs. Type I effectiveness-implementation hybrid designs prioritize clinical effectiveness outcomes (the design that we propose), type II balances effectiveness and implementation outcomes, and type III emphasizes implementation outcomes. Given that effectiveness research using non-specialist integrated care is in the early stages in this region, we will use a type I design. Randomizing at the participant level, we will emphasize collection of effectiveness data while gathering implementation data to advance an evidence base for sustainable, integrated depression care in LMICs

Research team: Based on our work in the region, we are aware that implementation research that achieves a sustained positive impact after study conclusion must include key stakeholders at national and local levels who make final decisions on the allocation of healthcare funds, and directors, providers, staff, patients and community liaisons at the proposed clinic(s). Therefore, we have in place a team with (1) academic and research

expertise in implementation science, healthcare economics, integration of mental health services within large Kenyan healthcare settings and task-shifting for delivery of evidence based depression care; (2) national and local healthcare policy and economics, including decision-makers for the allocation of healthcare funds (Drs. Simon Kahonge, David Bukusi and Dickens Onyango) (3) KCH and other Kisumu County Ministry of Health facilities directors and FACES KCH and other Kisumu County Ministry of Health facilities staff who have successfully integrated with primary care to provide over a decade of sustained service, and FACES' roster of contacts, including KCH and other Kisumu County Ministry of Health facilities providers, staff, patients and community advisory groups. See discussion of the EPIS model, below, for details on how we will form collaborative stakeholder implementation teams to plan and adapt the study (as needed) and strategy for incorporating positive findings into policy and practice.

Overview of our approach: The EPIS model will be our primary vehicle for engaging key stakeholders to plan the proposed research, adapt/optimize depression care and identify strategies for incorporating positive findings into policy and practice. The EPIS model balances engagement of the inner context (e.g., clinic staff, patients, providers) and outer context (e.g., local health policy and community leaders, regional stakeholders, national mental health policy experts) stakeholders (Figure 2). We will use the DAP to make contextually required adaptations in order to optimize the fit of depression care delivered by non-specialists and integrated with primary care without sacrificing fidelity to evidence based practice. The DAP process will be carried out by an implementation resource team (IRT) composed of stakeholders from the inner and outer settings and

representing the spectrum of collaborators, including community, academic and policy/government leaders.

Building on our team's experience with integration of mental health care services in Kenya,(Zunner et al., 2015)·(Verdeli et al., 2003) our first step will be to identify the key stakeholders from the "inner"(e.g. clinic staff, patients and providers) and "outer"(e.g. county and national health policy makers, community leaders and regional leaders) context of the proposed study. From these stakeholders, we will identify a diverse core implementation resource team, which will serve as liaisons and will participate in monthly adaptation process meetings to (1) review study protocols and trouble shoot implementation (e exploration phase); (2) prepare for study launch with communications and logistical preparations (EPIS preparation phase); (3) review study progress, deepen engagement with key stakeholders, monitor fidelity to protocol and identify areas in need of further adaptation (EPIS implementation); (4) as results accumulate, discuss best strategies for local dissemination of findings, and collaborative strategies to produce the most useful of final results to achieve maximal public mental health impact in Kenya and regionally (EPIS sustainment).

To explore optimal logistics for integration of depression screening and care into the adult outpatient clinics at Kisumu County Hospital (KCH) and other Kisumu County Ministry of Health facilities we will meet with patients, patient representatives, staff and heads of staff to identify optimal strategies for integrating depression care services within outpatient clinics in KCH and other Kisumu County Ministry of Health facilities, and by telephone. We will also collaborate with and learn from the experiences of the FACES teams at KCH and other Kisumu County Ministry of Health facilities, which currently

integrates with outpatient medical clinics to provide HIV services – drawing on the successes of their model. FACES also has a strong assemblage of community advisory groups (CAGs) composed of local religious leaders, patients of community health care and village chiefs who are experienced with review and advising on new healthcare endeavors. CAGs meet monthly, and we will put the addition of depression screening and care for KCH and other Kisumu County Ministry of Health facilities adult outpatients on the agenda, soliciting feedback on best strategies for communicating about the change, decreasing stigma and maximizing participation. In addition, we will leverage our current relationships with the local director of medical services and the national director of mental health in the MOH as well as the medical superintendents of KCH and other Kisumu County Ministry of Health facilities soliciting feedback on best strategies for optimizing public health impact. As preparation for the study launch proceeds, we will hire study personnel that are experienced with KCH and other Kisumu County Ministry of Health facilities adult outpatient clinics and can function as liaisons for sustainment. We will also work with Community Health Workers (CHWs) and Community Health Volunteers (CHVs) to mobilize and sensitize the community about mental health services and refer community members to one of the health facilities for screening for the SMART-DAPPER study. During implementation, we will meet regularly with local stakeholders, as well as the regional and national health policy leaders to share study progress. In the sustainment phase, we will discuss study findings and next steps for scale up of primary care integrated depression care services in Kenya. The implementation resource team will meet quarterly in person or by telephone with PIs and Co-Is and serve as liaisons from stakeholder groups on study launch, logistics,

findings and/or dissemination of results, with the goal of optimizing the utility of the final results for maximal public mental health impact in Kenya and regionally.

Study Procedures.

Participants in our proposed study – A sequential, multiple assignment randomized trial (SMART) for non-specialist treatment of common mental disorders in Kenya: Leveraging the Depression And Primary-care Partnership for Effectiveness-implementation Research (DAPPER) – will be initially randomized to 12 weekly one-hour sessions of IPT (3 months) or 6 months of fluoxetine (tapering up to 60mg). Those participants who are not in remission with at the conclusion of initial treatment will be re-randomized to second-line treatment (see below). Prior to randomization, participants will be given the option to receive their treatment at the health facility or by telephone. Participants who are randomized to fluoxetine and conduct their visits by telephone will need to collect their medication at the health facility. If participants do not collect their medication at the health facility, fluoxetine may be delivered to participants in the community. A smaller, Part 2, of the study will consist of qualitative interviews and focus groups to assess the overall implementation strategy and gather feedback on the specific interventions. Please see "Part 2," below (and additional consent for this aspect of the study, attached).

Randomization and blinding: Randomization will take place after baseline measures are complete. Randomization will be done in blocks of 10 and stratified by sex and telephone vs in-person treatment to ensure that the treatment groups are approximately equal in size and in gender distribution and telephone vs in-person treatment. See below

for second randomization information. Clinical evaluators who conduct follow-up assessments will be blinded to treatment assignment. Participants, IPT therapists, fluoxetine providers cannot be blinded because they will either be providing or receiving the IPT and/or Fluoxetine treatment and therefore they will know their treatment status. In addition, at least one study coordinator will not be blinded to assist with tracking of participants.

Study visits: To characterize the trajectory of symptom change during treatment, participants will be re-evaluated at the mid-point of treatment (month 1.5 for IPT and month 3 for fluoxetine). Treatment mid-point data is valuable because it can inform the minimum duration of treatment necessary to optimize mental health gains in a setting of scarce mental health resources. For example, if 90% of all observed treatment gains are achieved in the first half of treatment, subsequent implementation efforts might consider shortened courses of treatment. Participants will be assessed at month 3 (end of IPT treatment, mid-point of fluoxetine treatment) and at month 6 (end of fluoxetine treatment). For those participants who are in remission from depression and/or PTSD, follow up assessments will then continue at 9 month, 12 month and then at six month intervals until month 30 to assess for maintenance of gains and relapse. Assessments may be done at the health facility or by telephone. We are defining remission as absence of disease as defined by threshold criteria for Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) for PTSD and MDD. Those participants who have not yet remitted will be re-randomized to: switch of treatment (from IPT to fluoxetine or vice versa) or combination treatment (addition of IPT to fluoxetine or vice versa). See Figure 3.

Assessment schedule and rationale:

In order to characterize the trajectory of symptom change during treatment, participants will be re-evaluated at the mid-point of treatment (month 1.5 for IPT and month 3 for fluoxetine). Treatment mid-point data is valuable because it can inform the minimum duration of treatment necessary to optimize mental health gains in a setting of scarce mental health resources. For example, if 90% of all observed treatment gains are achieved by month 1.5, subsequent implementation efforts might consider shortened courses of treatment. Participants will be assessed at end of treatment (month 3 for IPT and month 6 for fluoxetine) and fluoxetine recipients will be tapered off the medication. At six months, participants will be re-assessed and then monitored at 6-month intervals until month 30 (Figure 3). Assessment visits may be done at the health facility or over the telephone.

Measures (Table 1): *Demographics.* We will obtain usual demographic measures, education, including individual income, assets, education and school fees, healthcare utilization, and time allocation.

Physical health co-morbidities. Given the strong association of depression with physical disorders, we will assess such as major medical co-morbidities in this population: HIV, malaria, hypertension and diabetes. We will also collect concomitant medication.

Accessibility. We will evaluate accessibility as defined above (geographic proximity to clinic, type and severity of challenge for attending depression appointments).

Affordability. We will assess cost of transportation to KCH and other Kisumu County

Ministry of Health facilities, and costs of treatment by telephone and opportunity costs for each treatment session.

Mental health. We are aware of the current discussions regarding categorical versus dimensional (RDoC) measures in mental health research.(Insel et al., 2010) However, to efficiently integrate mental health with KCH and other Kisumu County Ministry of Health facilities primary care outpatient clinics treating specific diseases (HIV, malaria, hypertension, diabetes), our procedures must be disease-specific. We will use a threshold criteria for DSM-V for MDD which we are currently using in our IPT study at the FACES-Lumumba site in Kisumu (Table 1). We will also use the Self-Assessment Manikin (SAM) (Bradley MM, 1994), Patient Health Questionnaire (PHQ-2) (Kroenke K, 2003) Primary Care PTSD Screen (Prins A, 2015), the Ask Suicide-Screening Questionnaire (ASQ)(Horowitz, L.M, 2020), the Mood Disorder Questionnaire (MDQ) (Hirschfeld R, 2000) and The Pandemic Emotional Impact Scale (Palsson O, 2020). Given the high rates of domestic violence, alcohol use disorders, and deaths due to disease such as HIV and the influence of traumatic events on depression etiology and treatment response,[e.g.,](Cattaneo et al., 2015) we will measure domestic violence, alcohol and drug use disorders, general trauma history and perceived social support (Zimet GD, 1988). *Health-related disability.* We will use WHO standard measures. All of the Table 1 measures have been translated into local languages (Luo and Kiswahili) as part of our current study, using a standardized process of measure adaptation and translation.(Bhui, Mohamud, Warfa, Craig, & Stansfeld, 2003; Bolton, 2001; de Jong & van Ommeren, 2002; Smit, van den Berg, Bekker, Seedat, & Stein, 2006; Sousa & Rojjanasrirat, 2011)The Trauma History Questionnaire and the Conflict Tactics Scale have both been

used in 2 ongoing studies in Kisumu, Kenya.(Onu et al., n.d.) These are a mixed method study whose main objective is to identify the mental health impact of providing testimony to FIDA legal providers for women with claims related GBV and a capacity Building Randomized Controlled Trial of Interpersonal Psychotherapy for HIV+ Women Affected by Gender Based Violence. The studies are not formal psychometric evaluation/validation studies, but show acceptability and convergent validity. As the results of those measures were corroborated by qualitative assessments. The BDI also showed convergent validity in Luo (as well as the Kiswahili) with the MINI MDD diagnosis.

Table 1: SMART-DAPPER Measures	
Variable	**Description**
Demographics	Age, gender, marital status
Highest education	(1) None; (2) primary; (3) secondary; (4) tertiary and beyond
Individual income and employment, education, assets, school fees, and time allocation	Assessment of individual formal and informal income and employment, assets, education, and time allocation
Health co-morbidities	HIV, Malaria, HTN, DM
Proximity to clinic*	Location of residence relative to KCH and other Kisumu County Ministry of Health facilities
Overall challenges for attending depression care appointments at KCH and other Kisumu County Ministry of Health facilities, and by telephone and identification of top challenge*	(1) easy challenge (2) moderate challenge (3) difficult challenge (4) impossible or nearly impossible challenge; (5) Identify source of the greatest challenge in text (e.g., money, logistics, stigma, etc.)
Cost of transport from residence to KCH and other Kisumu County Ministry of Health facilities, and any associated telephone costs **	(1) 0-100KSH (2) 100-300KSH (3) 300-500KSH (4) more than 500KSH

Opportunity costs per depression treatment session: lost wages, dependent care**	(1) 0-100KSH (2) 100-300KSH (3) 300-500KSH (4) more than 500KSH
Major Depressive Disorder (MDD)	Beck Depression Scale (BDI)(Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), MINI MDD module (D V Sheehan, 1998)
Post-traumatic Stress Disorder (PTSD)	Posttraumatic Stress Checklist (PCL-5), MINI PTSD module (D V Sheehan, 1998), Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) (Prins A, 2015)
Suicidality, mania/hypomania (exclusion-referral)	Beck Depression Scale (BDI)(Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), MINI suicidality, (hypo) mania modules (D V Sheehan, 1998), Mood Disorder Questionnaire (Hirschfeld R, 2000), ASK Suicide-Screening Questionnaire (ASQ)(Horowitz, L.M., 2020)
Depression symptoms	Beck Depression Scale (BDI)(Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), Patient Health Questionnaire-2 (PHQ-2) (Kroenke K, 2003)
Emotional reactivity	Self-Assessment Manikin (SAM) (Bradley MM, 1994)
Domestic violence	Revised conflict tactics scale (CTS2) (STRAUS, HAMBY, BONEY-McCOY, & SUGARMAN, 1996)
Trauma history	Trauma History Screen (THS)(Carlson et al., 2011)
PTSD symptoms	Posttraumatic Stress Checklist (PCL-5)
Detailed alcohol use (exclusion-referral)	Alcohol Use Disorders Identification Test (AUDIT)(Babor, Higgins-Biddle, Saunders, Monteiro, & World Health Organization, 2001)
Drug use (exclusion-referral)	Drug Abuse Screening Test (DAST-10)(Skinner, 1982)
Social Support	Multi-dimensional Scale of Perceived Social Support (MSPSS) (Zimet GD, 1988)
Health-related disability	World Health Organization Disability Assessment Schedule (WHODAS)(Üstün et al., 2010)
Wellbeing and functioning changes due to COVID-19 pandemic	The Pandemic Emotional Impact Scale (Palsson O, et al., 2020)
Depression And Primary care Partnership for Effectiveness-implementation Research (DAPPER); Diabetes Mellitus (DM); Human Immunodeficiency Virus (HIV); Hypertension (HTN); Kenyan Shillings (KSH) (100KSH~1USD); Major Depressive	

Disorder (MDD); Mini International Neuropsychiatric Interview version 5.0 (MINI v. 5.0). * Accessibility measures; **Affordability measures.

Non-specialist training and treatment refinements for context

● **IPT:** Based on our experience training local community members to deliver IPT in the proposed region of research and other LMICs,(Jiang et al., 2014; Meffert et al., n.d.; Onu et al., 2016; Zunner et al., 2015) we have developed a process of combining training in IPT with cultural adaptations, as needed, from IPT trainees.

Prospective IPT therapists will be identified according to the following criteria: (1) fluency in all local languages (Luo, Kiswahili) and English; (2) plans to remain in the area for the duration of the study with continuous availability to provide weekly therapy; (3) strong interest in providing mental health care; and (4) a promising background for effective communication regarding emotions (e.g., community healthcare workers, teachers, church leaders, women's group leaders, village chiefs, village elders, traditional healers, HIV treatment adherence counselors, formal health or mental health care training/experience). While primary care physicians, clinical officers and available mental health specialists will be actively recruited and welcomed, their level of healthcare experience will not be required for IPT therapists.

Prospective IPT therapists will be invited to join a 10-day IPT training course. The first 3 days of the course will consist of an introduction to mental disorders, focused on depression and trauma-related conditions and emphasizing a medical model. Patient-provider interactions will be reviewed, including the fundamental importance of confidentiality and respect. Basic tenets of psychotherapy and its evidence will be

introduced, followed by introduction to IPT and an overview of its initial, middle and concluding phases (Figure 4).

Refinements for use of IPT in primary care: [*Note: We have already adapted IPT for non-specialist, integrated delivery within a FACES HIV care setting in our current study. Here, we describe minor refinements to optimize logistics and content fit for primary care adult outpatient clinic served at Kisumu County Hospital, a FACES-supported clinic*].

Following the introductory training, we will begin an iterative process of more IPT training, using the trainee therapists (including local health care providers) as our primary resources. We will review the sequence of work, including tasks and techniques for each session and phase of IPT (Figure 4). During this detailed review, we will solicit feedback from local IPT trainees on cultural or logistical adaptations or additions needed to improve the acceptability and relevance of IPT for the target population.

An iterative group process will be used to integrate input from trainee therapists on adaptations of IPT content and process with ensuing modification if consensus is reached that not doing so would negatively affect outcomes or engagement. The adaptations defined through the above processes will be incorporated with the standard IPT manual to create adaptations tailored to the needs of KCH and other Kisumu County Ministry of Health facilities adult primary care outpatients. We will also develop standard operating procedures and provide training on adaptations for conducting IPT over the telephone including how to address a mental health crisis. Primary care physicians, clinical officers and available mental health specialists will be invited to participate as providers during the run in period of the study. Those showing consistently high protocol adherence and

interest will be recruited as onsite IPT supervisors, with oversight by the study PIs and Co-Is.

IPT therapist competency testing: When the IPT training concludes, prospective study therapists will be asked to articulate the fundamental tenets of IPT and to successfully model an example of an initial, middle, and concluding IPT session through role play with other trainees. If they demonstrate competency, therapists will be assigned an IPT practice case. If sessions are successfully completed with the training case, as demonstrated by scores of 9 or 10 on our 10-12 item IPT adherence measures, DAPPER IPT study participants will be gradually added to therapists' caseloads with a maximum of 10 clients per therapist.

- **Fluoxetine**

Antidepressants for MDD and PTSD: Research team members Drs. Wagner and Akena developed a clinical guide for non-specialists to provide antidepressant care on HIV platforms in a nearby region of Uganda.(Wagner, Ngo, Glick, et al., 2014; Wagner, Ngo, Akena, & Seggane, 2014) Drawing heavily on that protocol, we will train all interested nurses and clinical officers at the KCH and other Kisumu County Ministry of Health facilities adult primary care clinic and additional study providers to deliver fluoxetine to SMART-DAPPER participants.

Prospective fluoxetine providers will be invited to attend a 10 day training course. We will begin with an introduction to mental disorders, focused on depression. Patient-provider interactions will be reviewed, including the fundamental importance of confidentiality and respect. The use of antidepressants to treat depression and/or PTSD will be taught, with a focus on the role of fluoxetine. The dosing protocol will be

introduced, followed by review of potential side effects and required provider responses for each effect, including any uncertainty regarding existence or type of side effect. The importance of ruling out bipolar affective disorder before initiating fluoxetine (*see exclusion criteria*), will be emphasized and symptoms/signs of mania/hypomania will be reviewed. Role plays and case studies will be used to practice assessment, dosing and evaluation of side effects and/or mania/hypomania. We will also develop standard operating procedures and will also provide training on adaptations for conducting fluoxetine treatment visits over the telephone including how to address a mental health crisis. Primary care physicians will also be trained in fluoxetine treatment of MDD and/or PTSD, and recruited as providers during the run in period of the study. Those showing consistently high protocol adherence and interest will be invited to assist with onsite fluoxetine treatment supervision, with oversight by the study PIs and Co-Is.

Fluoxetine provider competency testing: The course will conclude with 10-20 case studies, in which prospective fluoxetine providers will be asked to apply the fluoxetine treatment protocol and respond to case scenarios including contraindications, side effects and dosing challenges. If they demonstrate competency on these tests, fluoxetine providers will be assigned training cases including starting and monitoring fluoxetine treatment. If they successfully complete training cases, as demonstrated by scores of 9-10 on fluoxetine protocol adherence measures, fluoxetine participants will be gradually added to the trained fluoxetine provider caseloads, to a maximum of 10 cases.

IPT and fluoxetine treatment schedule and location: IPT and fluoxetine appointments will be conducted at confidential location within the KCH and other Kisumu County Ministry of Health facilities, or over the telephone. IPT will be administered by an IPT

therapist (see therapist selection and training procedures, above), in 12 weekly 60-minute sessions. Participants randomized to receive fluoxetine will meet or speak with fluoxetine trained provider at baseline, 2 weeks, 4 weeks, 2, 3, 4, 5, and 6 months, for a total of eight appointments. Participants will be assessed for initiation of fluoxetine and advisement on common side effects. Fluoxetine participants will be started on 20mg (1 capsule per day) and will return for assessment of initial efficacy/tolerability at week 2. If the participant does not have any prohibitive side effects, dose will be maintained at 20mg (1 capsule). Participant will return for re-assessment at week 4, if the participant does not have any prohibitive side effects and does not have improvement on the Patient Health Questionnaire-2 (PHQ-2), dose will be increased to 40mg (2 capsule). At month 2, if the participant does not have any prohibitive side effects and does not have improvement on the PHQ-2, the dose will be increased to 60mg (3 capsule). Participants receiving treatment by telephone may be able to receive a 3 month supply at the minimum dose (20 mg per day). If the dose is increased during the intervening treatment visits, the participant will need to receive additional medication. Participants receiving treatment by telephone will be asked to pick up their medication within two days of their treatment call. If they do not collect their medication within 2 days, the medication will be delivered in the community. Studies support that higher fluoxetine doses do not show additional benefit.(Jakubovski, Varigonda, Freemantle, Taylor, & Bloch, 2016) See Protection of Human Subjects section for details on fluoxetine side effect management. The participant will be maintained at 20, 40 or 60 mg at the month 3, 4, and 5 visits, if the participant does not have any prohibitive side effects. At the month 6 visit, participants will be given instructions for tapering off fluoxetine, with decrease of the dose by 20mg

increments each week until reaching zero. Participants who were maintained on 20 mgs throughout the treatment period will have fluoxetine discontinued at the end of 6 months. IPT therapists and fluoxetine-trained providers will be compensated per IPT/medication session/day completed, at the local currency equivalent of 10usd.

Fluoxetine treatment duration: Participants treated with fluoxetine will be tapered off fluoxetine at month 6.

Retention: Based on previous work, retention is not expected to be a problem. Our pilot study of IPT for Sudanese refugees in Cairo had a 93% retention rate; our study of IPT for survivors of the Sichuan earthquake had an 85% retention rate and our ongoing study of integrated IPT care with HIV+GBV+ women in Kisumu has 300 enrollees with 20 dropouts (93% retention, to date). However, given uncertainty regarding generalizability to the KCH and other Kisumu County Ministry of Health facilities adult primary care clinics, the more conservative estimate of 20% drop-out will be used. However, provision of treatment over the telephone may improve retention rates. As part of retention efforts, participants will be asked to provide the name and phone number of a trusted adult who can be contacted if the study has concerns about participants' welfare or whereabouts. Therapists and fluoxetine providers will be asked to provide study cell phone numbers to study participants. Missed appointments will be followed with at least two efforts to reach the participant directly and/or through their contact (80% cell phone coverage). Likewise, at least two efforts will be made to reach drop-out participants for remaining measures.

Acute mental health care: IPT therapist and fluoxetine training will include risk assessment and referral procedures for acute mental health care needs. See Protection of Human Subjects section for details.

Clinical evaluators: Clinical evaluators will be blind to treatment group and will conduct baseline screening at the primary care clinic prior to initiating treatment, as well as re-assessments at months 1.5 (mid-treatment for IPT), 3 (mid-treatment for fluoxetine), 6, 9 month 12, 18, 24 and 30. Candidate clinical evaluators will undergo a two day training during which they will be introduced to the study measures and their proper application. At the conclusion of the training, the candidates will be observed in their administration of the measures, assessing for accuracy and completeness. If successful, they will be evaluated for reliability by conducting a group interview and comparing measure results. Those who demonstrate both accuracy and inter-rater reliability will be invited to join the study. Monetary compensation will be provided for completed measures at the local currency equivalent of 7usd.

Data collection. Data collection will use tablets programmed with Research Electronic Data Capture (REDCap), similar to the electronic data system that we are currently using in Kisumu, Kenya (Online Data Kit [ODK]). REDCap now has an offline feature which does not require internet connectivity for data entry and can be later connected to the internet for upload to secure server.

Effectiveness outcomes

Clinical evaluators. Clinical evaluators will consent and screen study participants, complete baseline measures and then refer participants to (un-blinded) study coordinators for randomization. Blinded to group assignment, clinical evaluators will conduct 1.5 month (IPT treatment mid-point), 3 month (IPT end-of-treatment, fluoxetine-mid-treatment), and follow-up assessments. Candidate clinical evaluators will undergo a two day training during which they will be introduced to the study measures and their proper application. At the conclusion of the training, the candidates will be observed in their administration of the measures, assessing for accuracy and completeness. If successful, they will be evaluated for reliability by conducting a group interview and comparing measure results. Those who demonstrate both accuracy and inter-rater reliability will be invited to join the study. Monetary compensation will be provided for completed measures at the local currency equivalent of 7usd.

Data analysis plan

For *Hypothesis 1a* the analysis is standard intention to treat for 3 month (end of treatment) data. Our basic analysis strategy will be to fit logistic regression models for the outcome of MDD and/or PTSD remission, in this case with the predictor of group assignment (IPT or fluoxetine), demographics and severity of baseline depression and/or PTSD symptoms (BDI and PCL) . *Hypothesis 1b* will be analyzed for the sub-group of participants who are in remission from MDD and/or PTSD at months 1.5 or 1.5 and 3 and will use weighted generalized estimating equations logistic regression to accommodate the repeated measures on this subgroup through month 30.

As identified by RDoC, current mental disorder disease categories may allow for diversity among psychological constructs of negative/positive valence, cognition, social processes and arousal/regulatory systems, undermining the utility of current disease definitions and average treatment responses for some individuals. Based on this concern, we will evaluate for heterogeneity in treatment response trajectories for individuals with MDD and/or PTSD using X^2 tests (binary outcome, [threshold for DSM-V for MDD yes/no; PCL yes/no]) and t tests (continuous outcome, [depression symptoms, BDI/ PTSD Symptoms PCL]) on key study outcomes. Next, we will use mixed-mode latent regression modeling to identify heterogeneous sub-group trajectories.(Haviland & Nagin, 2005) We will use the Bayes Information Criterion to identify the appropriate number of subgroups, deriving the smaller number.(Raftery, 1995)

Procedures and measurements to assess implementation approach (EPIS) and outcomes.

EPIS strategy. The feasibility, acceptability and utility of this study's EPIS strategy, including its use of a DAP to integrate the feedback from the implementation resource team (IRT) members into the delivery of evidence based depression treatment will be evaluated using semi-structured individual interviews and focus groups with inner and outer context IRT members, providers and study participants. Domains of interest. *IRT members* will be asked: (1) to identify positive and negative aspects of the EPIS model, IRT and DAP strategies, including content and process; (2) to identify ways to improve the DAP process. *Providers* (mental health and primary care) will be asked: (1) their awareness and understanding of the use of the EPIS model; (2) satisfaction or dissatisfaction with the EPIS, IRT and DAP strategies for adaptation of evidence-based

depression treatments in DAPPER; (3) suggestions for improvement. *Study participants* will be asked: (1) their awareness and understanding of the use of the EPIS model; (2) satisfaction or dissatisfaction with the EPIS, IRT and DAP strategies for adaptation of evidence-based depression treatments in DAPPER; (3) suggestions for improvement. Enrollment (n=112) and study procedures. 16 focus groups will be conducted with five participants each (n=80). Focus groups will include: (1) inner context IRT members at each EPIS stage (4 groups); (2) outer context IRT members at each EPIS stage (4 groups); (3) study participants in the implementation and sustainment phases (2 groups each phase, 4 total) and (4) study providers in the implementation and sustainment phases (2 groups each phase, 4 total). Thirty-two individual interviews (n=32) will be conducted with IRT members (2 interviews with inner and outer IRT members at each EPIS phase [n=16]), participants and providers (2 interviews with each group at each EPIS phase [n= 16]).

Implementation outcomes and mechanisms of action

Acceptability and appropriateness. The acceptability and appropriateness of IPT/fluoxetine for treatment of MDD and/or PTSD in primary care clinics will be assessed through semi-structured closing and post-implementation of tele-mental health interviews and focus groups with participants, IPT therapists, providers delivering fluoxetine, KCH and other Kisumu County Ministry of Health facilities primary care clinics and FACES personnel and FACES CAGs. Domains of Interest. *Participants* will be asked: (1) to identify positive and negative aspects of IPT and fluoxetine treatment, including content, delivery, logistics; (2) if they would refer other people to the treatment

and why; (3) if they prefer IPT or fluoxetine treatment of MDD and why; (4) to identify suggestions for improvements; (5) feedback on tele-mental health. *IPT therapists and providers delivering fluoxetine* will be asked: (1) if they believed IPT/fluoxetine benefitted participants and why; (2) whether they would like to continue providing IPT/fluoxetine; (3) what suggestions they have to improve the intervention; and (5) feedback on tele-mental health. *Primary care clinic personnel, KCH* and other Kisumu County Ministry of Health facility *directors, KCH* and other Kisumu County Ministry of Health facility-*based FACES personnel, local and national healthcare policy makers,* will be asked: (1) to identify positive and negative aspects of IPT and fluoxetine treatment, including delivery, logistics; (2) to identify positive and negative impacts of treatment on primary care clinic and community; (3) whether or not they would like continuation of IPT and/or fluoxetine treatment for MDD and/or PTSD in their community and why/why not; (5) feedback on tele-mental health; and (6) suggestions for improvement of either treatment.

Enrollment (n=65) and Study Procedures. Nine focus groups will be conducted with five participants each (n=45). Focus groups will include: (1) Study participants who completed IPT or fluoxetine (one group each); (2) Prospective participants who declined enrollment; (3) enrolled participants who dropped out during treatment; (4) IPT therapists and fluoxetine providers (one group each); (5) primary care personnel; (6) FACES-KCH and other Kisumu County Ministry of Health facilities staff; (7) health policy leaders at the county level. Twenty individual interviews (n=20) will be conducted with participants (including those who decline enrollment, drop out of treatment and treatment-completers), depression care providers, primary care clinic personnel, KCH and other

Kisumu County Ministry of Health facilities directors and local and national policy makers.

Concept Mapping. We will use the IRT and extended IRT members to inform study related implementation questions using concept mapping methods. Concept Mapping is a process that allows stakeholders to express their ideas on a given topic, examine how these ideas relate to one another, and determine what ideas are judged to be most important or critical for a particular goal or initiative. Concept Mapping has three activities all to be completed online: 1) begins with a brainstorming process in which participants respond to a focus statement, 2) each participant is provided with a complete set of the statements and asked to sort them into categories based on similarity, and 3) each participant will rate statements.

Feasibility. Attrition from the study will be evaluated in regards to both timing (active treatment or follow-up phase) and reason (e.g., symptom remission, move out of the region, lost wages/dependent care, cost/burden of transport, displeased with treatment). With the exception of those who leave the study because their symptoms remit ("cured"), the IPT/fluoxetine will be considered feasible if fewer than 20% of participants leave during treatment and if one or fewer therapists/fluoxetine provider voluntarily leave the study.

Fidelity

Therapist Adherence to IPT Protocol. Therapists will discuss each IPT session with a supervising clinician. During supervision, therapists will be assisted with their adherence to and application of IPT. Adherence will be scored using a 10 point Likert scale assessing adherence in each IPT phase (used in our current IPT study). Sessions will be

considered adherent to the IPT protocol if they average a score of 5 or higher and do not employ off-protocol interventions. All sessions will be audio-taped and 20% of sessions will be selected using blocked randomization to ensure both early and late sessions are included, then transcribed and translated for IPT adherence scoring by an independent rater.

Fluoxetine Provider Adherence to Fluoxetine Protocol. In collaboration with the study coordinators, Drs. Ongeri and Akena (co-Is) will randomly select 10 charts of treated patients each month to assess compliance with the fluoxetine treatment protocol (eligibility, dosing and monitoring of side effects). Treatment will be considered adherent if there are no deviations from protocol.

Acceptability and Appropriateness. Interview material will be recorded in audio files, transcribed and translated. Dedoose software will be used to analyze the resulting text using grounded theory. Grounded theory sorts data in three ways: through concepts, categories and propositions. Concepts are identified by seeking conceptual similarities among focus groups/interviews. These concepts are grouped to develop categories of concepts. Categories are then compared and grouped to develop propositions or theoretical constructs about the phenomena of interest. Dedoose software facilitates coding of observations to work toward the theoretical construct. Data will be collected using a "triangulation" technique that compares information from various sources (focus groups, individual interviews) in order to increase the reliability and validity of the findings. *Feasibility and Fidelity.* Feasibility and fidelity measures will be assessed by sample means and proportions, with 95% confidence intervals, and compared to pre-specified benchmarks (above).

Service delivery mechanism: availability and affordability. *Hypothesis 1c* will be addressed by calculating RE-AIM for IPT and fluoxetine according to the procedures outlined in Glasgow et al.(Glasgow, Vogt, & Boles, 1999) Then, we will then evaluate how RE-AIM scores correlate with availability and affordability measures (Table 2) for IPT versus fluoxetine. Finally, we will evaluate for mediation by treatment completion. Specifically, we will begin with logistical regression models of RE-AIM score including availability factors and affordability factors. If any significant relationships exist, we will construct figures of hypothetical relationships between variables that are significantly associated with RE-AIM score and create path diagrams, using effect sizes to identify potential causal pathways between availability, affordability and RE-AIM scores for IPT versus fluoxetine.

Table 2: Calculating RE-AIM from an Effectiveness-Implementation Hybrid Type I (SMART-DAPPER)(Farris, Will, Khavjou, & Finkelstein, 2007; Glasgow, Klesges, Dzewaltowski, Estabrooks, & Vogt, 2006)	
1	Reach will be calculated as the ratio of study participants who are eligible for SMART-DAPPER compared with those who choose to participate. ***R**each is the first assessment of **RE-AIM.***
Effectiveness Outcomes	
2a	MDD and/or PTSD remission from IPT or fluoxetine at month 3 (IPT) and month 6 (fluoxetine).
2b	MDD and/or PTSD remission at month 1.5 (treatment mid-point) for IPT and at 3 months (treatment mid-point) for fluoxetine to identify the proportion of treatment gain achieved at mid-point compared with end of treatment (month 3). Treatment ***E**ffectiveness is a key aspect of **RE-AIM.***
3	Maintenance of month-3 remissions from IPT or and month 6 remissions from fluoxetine at follow-up assessments (months 6 (for IPT), 9, 12, 18, 24 and 30). Maintenance of gains is an *individual level measure of **M**aintenance in **RE-AIM.***
Implementation Outcomes	
4	Both IPT and fluoxetine will be <u>acceptable</u> treatments for delivery in primary care as determined by qualitative interviews.
5	Both IPT and fluoxetine will be <u>appropriate</u> treatments for delivery in primary care as determined by qualitative interviews.

6	Both IPT and fluoxetine will be <u>feasible</u> treatments as determined by completion rates. *With the exception of those who leave the study because their symptoms remit, completion rate will be used as an individual level measure of **A**doption in **RE-AIM.***
7	Both IPT and fluoxetine will have strong treatment <u>fidelity</u> as determined by protocol adherence to IPT and fluoxetine administration. *Fidelity is a key component of **I**mplementation in **RE-AIM.***

Measurement of implementation costs. We will measure the full resources and associated costs of implementing the screening for MDD and/or PTSD in the KCH and other Kisumu County Ministry of Health facilities primary care adult clinics as well as the IPT and fluoxetine treatments for those who screen positive. Costs will include staff time as well as supplies (including drugs), services, telephone expense, and infrastructure used to deliver the interventions. Data on costs will be collected using two methods. The first will be <u>micro-costing</u> to quantify resources used and unit costs, with data extracted from project expenditure and management records, including purchase logs and human resource records. This information will be recorded in structured costing spreadsheets that capture each resource (e.g., space for IPT sessions and fluoxetine monitoring, telephone expenses), category (e.g., personnel, supplies), quantity (e.g., hours), and unit costs. A second method will be <u>time and motion logs</u> will record how staff divide time among multiple roles to allow us to reliably apportion effort to the mental health screening and treatment activities. Cost per person treated will be computed for IPT and also for fluoxetine treatments.

Measurement of economic effects on patients. We will also measure patient-level costs and benefits, including costs associated with transportation to clinics (included as part of treatment) and costs of using the telephone, and benefits such as increased labor supply and income. These measures will come from surveys administered at baseline and at follow-up (months 1.5, 3, 6, 12, 24 and 30). We will use a measure (Table 1) similar to

that which we are using to assess informal and formal income in our current effectiveness-implementation study in Kisumu, and that our research team is using across East Africa to assess the economic impacts of other health interventions. Employment gains in the informal and agricultural sectors will be converted to monetary values using imputed wages in the local labor market. Based on prior research that shows a strong linkage between mental health and economic outcomes,(Lund et al., 2011) we believe that assessing the economic benefits of depression treatment is essential for conducting a comprehensive cost-benefit analysis. To the extent that treatment results in changes in mortality (all-cause, whether or not suspected as suicide), we will incorporate these effects using the "full income" approach(Jamison et al., 2013), which attaches a financial value to each year of life lost.

Estimation of non-intervention control. For ethical reasons, our study does not include a non-treatment control. However, for complete cost-benefit analysis, we will compare the interventions to current (mainly absent) depression management. We cannot compare patients to their own baseline condition, since the natural history of untreated depression involves (at least episodic) clinical resolution in a substantial subset of individuals.(Whiteford et al., 2013) Instead, we will apply findings on the association of evolving clinical status and economic status in the intervention arms to historical data on the natural history of depression in these settings. In other words, we will make the conservative assumption that the changes in productivity associated with clinical resolution of the depression episode following treatment can be applied to untreated patients who eventually remit.

Cost-benefit analyses. An important question for policymakers concerns the economic returns to investments in treating and improving mental health. We will use data obtained on the economic status of those treated to calculate the economic benefits associated with treated mental health disorders (both pooled analyses of IPT or fluoxetine treatment and separate analyses of IPT and fluoxetine treatment). We will also incorporate data on health care utilization and hospitalizations (Table 1). The value of these economic benefits will be summarized on a per-person basis and then combined with the implementation cost data to generate a rate of return on mental health expenditures (in general and by treatment type –IPT or fluoxetine). This rate of return is net gains in all economic measures divided by implementation costs, x 100 to yield % return. Cost and income measures will be adjusted for inflation and discounting during the 3 year study period.

Human participants in the project

Target population. Adult primary care outpatient clinic attendees at Kisumu County Hospital (KCH) and other Kisumu County Ministry of Health facilities.

Sample size calculations: SMART designs are used to inform the construction of optimal Adaptive Treatment Strategies (ATS), which is our goal. Therefore, we will power our study to detect the smallest difference between the various ATS included in the study design. The proposed SMART examines (1) first line treatment strategies with IPT or fluoxetine, including long-term relapse risk for participants who remit with initial treatment and (2) second line treatment strategies for non-remitters—specifically, treatment "switch" (from IPT to fluoxetine or vice versa) versus treatment "combination" (addition of IPT to fluoxetine or vice versa). Based on the current evidence base, we

expect that differences between switching or combining treatment will be smaller than other ATS comparisons in the study and we will therefore power the study to detect this difference.

As it pertains to antidepressants and psychotherapy, the evidence base comparing "switching" versus "combining" treatment for non-remitters (second line treatment) is still developing. However, the field does have meta-analytic data on the differences between treating depression with antidepressants or psychotherapy alone, versus their combination. A 2009 meta-analysis (n=2036) which compared combination treatment (psychotherapy and pharmacotherapy) to pharmacotherapy alone for depression found an effect size of 0.31 (Cohen's d).27A 2007 meta-analysis (n=903) found that the remission rate for major depression treated with psychotherapy and pharmacotherapy was better than psychotherapy alone, with an odds ratio of 1.5928, which when converted to a Cohen's d is 0.25.29 While specific studies have not yet been completed for IPT and PTSD, we leveraged the above-referenced meta-analyses of the effects of general psychotherapy and general pharmacotherapy to estimate sample size for the proposed study. Based on those studies, we would need approximately 164 per treatment arm to compare combined psychotherapy-medication treatment with medication alone, and 242 to compare combined psychotherapy-medication with psychotherapy, alone (using a two-sided alpha of 0.05 and power of 0.80). Using the conservative estimate, we will need 242 for each of the four treatment arms (968, total) after the second randomization (switch to fluoxetine, switch to IPT, combination after fluoxetine, combination after IPT). Note, this strategy uses fluoxetine treatment for 6 months as a first line treatment,

consistent with the original R01 submission and responsive to reviewers' comments (summary statement response) on our funded U01 (DAPPER) study. While effectiveness data on treatment of depression in HICs (STAR*D) indicate that only approximately one-third remit with first line treatment, preliminary data from our current IPT study in Kisumu indicate remission rates over two-thirds. We will use a conservative estimate of the numbers entering the second randomization phase (non-remitters) and assume that half of study participants will need second-line treatment. Based on that estimate, the 968 participants randomized to the second stage of the SMART should represent 50% of those enrolled at the start of the trial, or 1936. Allowing for a 40% drop out rate across the 33 month duration of the study (domestic migration is common in Kenya30), we will need 2710 participants for the SMART.

The additional number required for integration of the SMART design is 710 participants. Making a conservative assumption of ~20% prevalence of MDD and/or PTSD among primary care patients, we will screen 3,550 individuals to enroll 710 participants. While KCH and other Kisumu County Ministry of Health facilities see over 10,000 adult primary care patients per month, we will assume that only 20% of clinic attendees will undergo screening, and we will budget 3 months for recruitment. In order to avoid overwhelming mental health care providers, these 3 months of recruitment will be dispersed across a 18 month period: enrollment will halt when providers' caseloads are full and resume when at least 20% availability is regained. We will also work with Community Health Workers (CHWs) and Community Health Volunteers (CHVs) to

mobilize and sensitize the community about mental health services and refer community members to one of the health facilities for screening for the SMART-DAPPER study.

Eligibility criteria

Inclusion criteria:

(1) KCH and other Kisumu County Ministry of Health facilities adult primary care outpatient clinic attendees who meet the threshold criteria for DSM-V for MDD and/or PTSD. .

(3) Ability to attend weekly IPT sessions/fluoxetine monitoring in person or by telephone;

(4) 18 years or older.

Exclusion criteria:

(1) Cognitive dysfunction compromising ability to participate in IPT or accurately take fluoxetine (lack of orientation to person, place, time and situation);

(2) Acute suicidality (moderate or high score on the MINI suicidality module or Ask Suicidality-Screening Questionnaire (ASQ)) requiring higher level of care;

(3) drug/alcohol use disorders requiring substance use treatment (AUDIT score of 8 or higher or DAST score of 3 or higher);

(4) History of mania or requiring treatment for bipolar affective disorder hypomania (positive score on MINI mania/hypomania module or on the Mood Disorder Questionnaire (MDQ));

(5) Outside mental health treatment during the SMART-DAPPER treatment phases (any mental health treatment is allowed during follow-up phases and is recorded by study team). Participants will be asked to not start new mental health treatment during the SMART-DAPPER treatments, but will be assured that this is not prohibited. Participants who do will be treated as dropouts.

(6) Pregnant or breastfeeding

Recruitment

Working closely with clinic directors, providers and staff, we will integrate with the KCH and other Kisumu County Ministry of Health facilities primary care adult outpatient clinics. Waiting times for primary care medical outpatients at KCH and other Kisumu County Ministry of Health facilities can last many hours, creating an opportunity for study recruitment. As with our current study, we will provide health talks to waiting room attendees regarding emotional distress and the availability of treatment services for eligible participants through SMART-DAPPER, inviting interested individuals to meet with our study team in a private area for more information, consent and screening, as desired. A recruitment poster, brochure, and/or cards will be made available with key information about the study including the contact information to reach for further information. If individuals wish to undergo study screening while waiting for their appointment, we will work with the clinic to provide them with a card that will allow them to enter back in the waiting line without losing their place, or moving them to head of the line if their name was called during their time with our team. Prospective

participants who consent, meet study criteria, and wish to enroll will be provided with an appointment date and time for baseline measures. If they do not consent, meet criteria and/or wish to enroll, they will be provided with information on alternative treatments (see Human Subjects). Per below sample calculations, allowing for holidays and time to integrate study procedures with primary care activities, we estimate that recruitment will last 18 months.

Given the large unmet need for depression and PTSD treatment, we will allow other public sector primary care centers and CHWs to refer individuals to the SMART-DAPPER study at KCH and other Kisumu County Ministry of Health facilities to receive mental health services, if eligible. Other recruitment strategies may be utilized to reach our recruitment targets. These other recruitment strategies may include sending text messages to patients receiving HIV care and treatment services at Kisumu County Ministry of Health facilities notifying them about the study and study requirements. We also may use social media and traditional media to inform the community about the study. Patients at other public sector primary care centers can also self-refer to the SMART-DAPPER study. All screening and enrollment will be conducted at KCH and other Kisumu County Ministry of Health facilities, or by telephone.

Mental health crisis. During recruitment, participants who report suicidality will be administered a Risk Assessment. Participants who are acutely suicidal will be escorted to KCH or another Kisumu County Ministry of Health facility psychiatric clinic for further evaluation.

Tracking team. FACES has a robust tracking team of employees who are highly knowledgeable of the local communities. FACES HIV patients who do not present for scheduled visits are contacted by the tracking team to assist with access to care. Leveraging their community contacts and the highly interconnected nature of communities served by FACES, efforts to contact the patient include phone calls, community and home visits, contacting relations and seeking out the individual at other medical appointments. For the proposed study, we will add similarly qualified SMART-DAPPER team members and CHW/CHVs to the ongoing KCH FACES tracking teams, to track SMART-DAPPER study participants who do not present for appointments.

Research Ethics

Institutional Review Process: This proposal will be reviewed by the KNH-UoN ERC the University of California San Francisco Institutional Review Board, National Commission for Science, Technology and Innovation (NACOSTI), and the Pharmacy & Poisons Board and granted approval before implementation.

Consenting Process:

All Participants: Informed consent will be obtained from prospective participants. Consenting will be performed without undue pressure or coercion. Only those who provide consent will be recruited in the study. Once the participant has been recruited, the clinical evaluator will explain the study and if s/he has accepted to be consented, the consenting process will be begin. We shall ask the participant the language they will prefer to use. We shall answer all the questions that the participants asks to help them

make informed decision. Those who decline to participate after reading the consent document will be thanked for their time, and those who agree to participate will be sign the consent form (if in person), or if we are unable to meet face to face to sign the consent form due to COVID19, the clinical evaluator will sign the consent form on their behalf.

The written consent procedures are as follows

1. The clinical evaluator will ask whether they want assistance in reading or they would do it themselves. The clinical evaluator or potential participant will read the entire consent form in its entirety (same information for written and verbal consent) in their preferred language;

2. Through the consent process, the clinical evaluator will ensure that the prospective participant understands each section in the consent before moving on by asking her or him to repeat it in his or her own words. The prospective participant must understand the nature of the procedure, the risks, benefits, and has the opportunity to ask and have questions answered;

3. Given the variable literacy levels, participants consenting will provide either a signature or a thumbprint to indicate their agreement with the consent. The clinical evaluator will also sign and date the consent form.

4. The participant will be offered a copy of the paper consent form.

5. Document in the research file (REDCap) where (in person) and when the consent discussion took place and if there were any issues.

Verbal consent procedures are as follows:

1. The clinical evaluator reads the entire consent form to the potential participant in its entirety in their preferred language (same information for written and verbal consent);

2. Through the consent process, the clinical evaluator will ensure that the prospective participant understands each section in the consent before moving on by asking her or him to repeat it in his or her own words. The prospective participant must understand the nature of the procedure, the risks, benefits, and has the opportunity to ask and have questions answered;

3. The prospective participant gives verbal agreement for study participation and the clinical evaluator will sign and date the verbal consent form.

4. The participant will be offered a copy of the paper consent from to be retrieved at the KCH and other Kisumu County Ministry of Health participating in the SMART-DAPPER study.

5. Document in the research file (REDCap) where (over the telephone) and when the consent discussion took place and if there were any issues.

Voluntariness: The participants will be informed that they will be free to withdraw from the study at any point without any untoward consequences and that participation is voluntary. Those who withdraw will still benefit from necessary care that will be available.

Confidentiality: All the interviews will be conducted individually and confidentially. Information collected will not obtain participants identifiers. Information entered in the

computers will be password protected. All hard copy documents with identifiers will be kept in lockable cabinets and will only be accessible to the study investigators.

Risks and benefits of the study

Risks to the Subject

Potential Risks
Risks and solutions related to inclusion/exclusion criteria at primary care referral clinics:

Inclusion:

If prospective participants meet the DSM-V threshold for MDD and/or PTSD, but no longer meet criteria when they present for SMART-DAPPER treatment, the common process of spontaneous remission will be discussed and they will be provided with contact information for the study coordinator, should their symptoms re-emerge. They will also be alerted to alternative mental health treatment options (see below).- If participants are unable to attend weekly appointments for 12 weeks for IPT or 8 sessions for fluoxetine (6 months), they will be alerted to alternative mental health treatment options in the area.

- If participants are not over the age of 18 years, they will be alerted to alternative mental health treatment options in the area.

Exclusion:

- Prospective participants who are identified as having cognitive dysfunction will be referred to primary care providers for work-up and treatment.

- Prospective participants with acute suicidality, will be escorted by our study team to the psychiatric facility for further evaluation and treatment.

- Prospective participants with substance use disorders with elevated scores on the AUDIT (8 or higher) or DAST (3 or higher) will be escorted by our study team to the nearest psychiatric facility for further evaluation and treatment.

- Prospective participants who have a history of mania or bipolar affective disorder will be screened for a current or past manic and hypomanic episode. If they have current symptoms, they will be escorted by our study team to the nearest psychiatric facility for further evaluation and treatment.

- Participants will be asked to not engage in mental health care outside the study during active treatment, but will be assured that they are not prohibited from doing this. They will also be told that they can use whatever type of mental health care they would like during the monitoring and follow-up phases of the study. They will be asked to alert study care provider and/or study coordinator if they begin receiving care outside the study and describe the type of care. If subjects do engage in outside mental health treatment during the SMART-DAPPER trial, they will be handled as a dropout at the point of engagement with the additional treatment.

- Pregnant and breastfeeding women will be excluded from the study given risk of fluoxetine in pregnancy and breastfeeding. These women will be invited to be screened for the study again after the conclusion of pregnancy and/or breastfeeding.

Adequacy of Protection against Risks
Recruitment and Consent Procedures:

Aim 1.

KCH and other Kisumu County Ministry of Health facilities primary care patients age 18 or older will be recruited to participate in mental health screening using procedures adapted from our current mental health treatment studies in the same city, including a "health information talk" in which information on the study will be provided to primary care patients waiting to be seen by KCH and other Kisumu County Ministry of Health facility providers, or referred by CHWs. Other recruitment strategies may be used including sending text messages to patients receiving HIV care and treatment services at Kisumu County Ministry of Health facilities notifying them about the study and study requirements. Social media and traditional media to inform the community about the study. Those who express interest will be invited to a private room for more information and a card system with KCH and other Kisumu County Ministry of Health facility providers will be used to ensure their place in the primary care patient cue. The first part of the meeting will be devoted to explaining the content and purpose of the study and completing a **written, informed consent,** if the prospective participant is interested and over the age of 18. Prospective participants may also be screened and verbally consented over the phone during the COVID-19 pandemic. Prospective participants will be alerted that, if they meet the threshold for DSM-V for MDD and/or PTSD and meet other eligibility criteria, they will be offered a referral to the SMART-DAPPER study for treatment, which will involve randomization to one of two evidence-based treatments delivered by a non-specialist. Those who meet inclusion criteria will be provided with an

appointment time and travel voucher (if conducting the visit in person) for completion of screening and baseline measures, as indicated.

When prospective participants who meet the threshold for DSM-Vfor MDD and/or PTSD present for care at the primary care referral clinic or by phone, they will again meet with our study staff in a private space before initiating treatment. Prospective participants will be informed that the process begins with a screening procedure which includes questions about their age, their ability to attend weekly 60-minute treatment sessions in person or by telephone and symptoms of depression. They will be informed that if they do not meet the eligibility criteria, they will not be enrolled in the study and if they have certain mental health risk factors, such as acute suicidality, bipolar affective disorder, or substance use disorders, they will be referred for higher level or different care. Potential participants will be informed that some of the questions may remind them of traumatic life experiences, emotional distress and problems in their relationships, and it is possible that these questions could be upsetting. They will be informed that they have the right to ask for a halt of the questions or treatment at any time. If the participant agrees to participate, the last stage of the interview will be devoted to completing the screening procedure and baseline measures (as indicated), providing further information regarding the study and answering questions about the study. The principles for overriding confidentiality will be made clear as defined below.

B. Protection Against Risk

Safety of Participants

Potential participants will be advised of the study principles of overriding confidentiality for the purposes of acute mental health care in three situations: risk of self-harm, risk of harm to others and grave disability (inability to provide for one's own food, clothing or shelter) secondary to mental illness. The personal safety of prospective study participants will be assessed during the completion of the screening process.. Any participants who respond affirmatively to suicidality will be further assessed using a suicidality screen. Those scoring moderate or high will be referred to by the PI, Co-I or designated crisis evaluation representative, who will be onsite for the duration of the study. Our current study with Family AIDS, Care and Education Services (FACES) has developed a robust mental health crisis response team composed of senior IPT therapists and study coordinators, with crisis protocols and referral channels, supported by the current study's PI and site PI (Drs. Meffert and Ongeri, respectively) and has operated without any adverse events, handling 1-2 crises per month over the last 1.5 years at the FACES-supported primary care clinic in Kisumu. Funds have been allocated to assist with immediate transport for urgent mental health care needs, with study team escort.

Mental Health Safety during Screening.

If the initial measures completed at KCH and other Kisumu County Ministry of Health facility primary care clinics or by phone suggest that a potential participant is at risk of self-harm, risk of harm to others or grave disability (inability to provide for one's own food, clothing or shelter) secondary to mental illness, or needs a different type of mental health care, he/she will be evaluated by our mental health crisis team and referred to higher level or alternative treatment, as needed. Potential participants will be informed that their mental health status will be evaluated at every IPT or fluoxetine monitoring

session. If their mental health status worsens during treatment such that they are at risk of self-harm, harm to others or grave disability, they will be re-evaluated, referred and escorted to a higher level of care/alternate care, as indicated.

Potential adverse events and proposed interventions

Nature and Degree of Risk: It is possible, that screening questions and/or additional measures applied at the primary care clinic could lead to emotional distress by reminding prospective participants of negative events or emotions.

While fluoxetine is considered a safe and well-tested selective serotonin reuptake inhibitor (SSRI), it is possible that subjects will have side effects or adverse effects from the medication, if they are randomized to receive it. Side effects of fluoxetine include nausea, sleepiness, headache, tremor, diarrhoea, nervousness, dry mouth, inability to sleep, and transient increase in suicide ideation.

While IPT is an evidence-based treatment for MDD and/or PTSD, with any psychotherapy some recipients can experience transient, initial elevation of symptoms as they begin acknowledging negative emotions.

Minimization of Risk:
Mental Health Safety during treatment

As part of study enrolment, potential participants will be asked “If we think you are in serious mental health trouble, whom we should call?” Name and number of supportive friend or family member will be gathered and used in the event of mental health crisis, in addition to mental health referrals. If the need for acute mental health care arises during screening or later in the treatment, this individual will be contacted to provide additional support. IPT and fluoxetine are expected to decrease psychiatric symptoms. IPT and

fluoxetine have been safely and successfully delivered by non-specialists in East Africa. IPT therapist and fluoxetine training will include evaluation of suicidality using the MINI suicidality module. Additional protections for urgent mental health care for participants receiving treatment over the telephone have been integrated. Protections include contacting the trusted contact, follow-up in person meeting with the treatment provider, and utilizing the treatment provider, retention tracker, and other study personnel if immediate tracking is needed.

Monitoring and response to fluoxetine side effects

Participants will be advised on common side effects with fluoxetine, including the potential for weight gain, sexual dysfunction and transient, initial nausea. They will be advised of less common, but possible side effects including suicidal thoughts, activation/agitation, insomnia, or sedation.

If participants experience severe side effects such as anxiety/activation, insomnia, suicidality, disabling sedation or significant weight gain/sexual dysfunction, their dose will be reduced to the lowest tolerable or they will be tapered off fluoxetine and they will be monitored with twice weekly visits and interim phone contact until stabilization is achieved, or they are referred for a higher level of care. Funds have been allocated to assist with immediate transport for urgent mental health care needs, with study team escort.

Potential benefits of the proposed study to participants and others:

Introducing the concept of mental disorders and screening primary care patients for depression may help to normalize the disorder and reduce stigma for affected individuals,

allowing them to access care with fewer social barriers. Providing referral appointments for those who screen positive for depression disorders may instill hope in the idea that the disorders are not shameful and that symptoms can be relieved with medical treatment.

Training local non-specialists to provide IPT and fluoxetine for MDD and/or PTSD may normalize the disorders for KCH and other Kisumu County Ministry of Health facility primary care providers. This could reduce stigma for affected individuals. Training local non-specialists to deliver evidence based care could demonstrate the feasibility of local, effective treatment of mental disorders and instill hope for patients and providers.

Adverse Events Treatment:

If participants experience severe side effects from Fluoxetine treatment such as anxiety/activation, insomnia, suicidality, disabling sedation or significant weight gain/sexual dysfunction, their dose will be reduced to the lowest tolerable or they will be tapered off fluoxetine and they will be monitored with twice weekly visits and interim phone contact until stabilization is achieved, or they are referred for a higher level of care.

Adverse Events Facilities: Resources for mental health crisis and alternative mental health care.

Resources for mental health care needs include evaluation and treatment with medication through KCH and other Kisumu County Ministry of Health facilities medical professionals and local resources for psychiatric care across a spectrum of diagnoses and severity (domestic violence crisis clinic, outpatient psychiatric clinic, inpatient psychiatric hospital ward). If the need arises for psychiatric hospitalization or mental

health care needs exceeding local resources in Kisumu county, Drs. Linnet Ongeri (Co-I), David Bukusi (Co-I) and Muthoni Mathai (PI), all of whom are practicing psychiatrists in Kenya with referral access to the nation's largest inpatient unit in Nairobi at Mathari Teaching and Referral Hospital, will be contacted for facilitation of specialist services.

a) **Financial Responsibilities**: Funds will be allocated to assist with immediate transport for urgent mental health care. Participant will be accompanied to the referral site by study staff.

Confidentiality of research data

The study records will be kept as confidential as is possible under the law. No individual identities will be used in any reports or publications resulting from the study. All participants will be assigned a unique participant identification number that will only be known to the PI and research staff. The key, with numbers corresponding to first and last names of participants, will be kept in a locked office and uploaded to a secure server on a Research Electronic Data Capture (REDCap) server hosted at UCSF, accessible only to study coordinators and PIs. REDCap's capability for offline data entry will be used with encrypted tablets, with later use of a secure internet connection to upload data to local, servers and a secure UCSF server. No participant personal identifiers will be entered in the REDCap data base

Ethical consideration:

Institutional Review Process: This proposal will be reviewed by the KNH-UoN ERC and the University of California San Francisco Institutional Review Board and the National Commission for Science, Technology and Innovation (NAOSTI) and granted approval before implementation. The study has also been approved by the Kenya Pharmacy & Poisons Board (PPB).

Consenting Process: Written Informed consent will be obtained from all prospective participants. Verbal consent may be conducted during the COVID-19 pandemic to avoid disease transmission. Consenting will be performed without undue pressure or coercion. Only those who provide consent will be recruited in the study.

Voluntariness: The participants will be informed that they will be free to withdraw from the study at any point without any untoward consequences and that participation is voluntary. Those who withdraw will still benefit from necessary care that will be available.

Confidentiality: All the interviews will be conducted individually and confidentially. Information collected will not obtain participants identifiers. Information entered in the computers will be password protected. All hard copy documents with identifiers will be kept in lockable cabinets and will only be accessible to the study investigators.

Additional information

Audio Recording

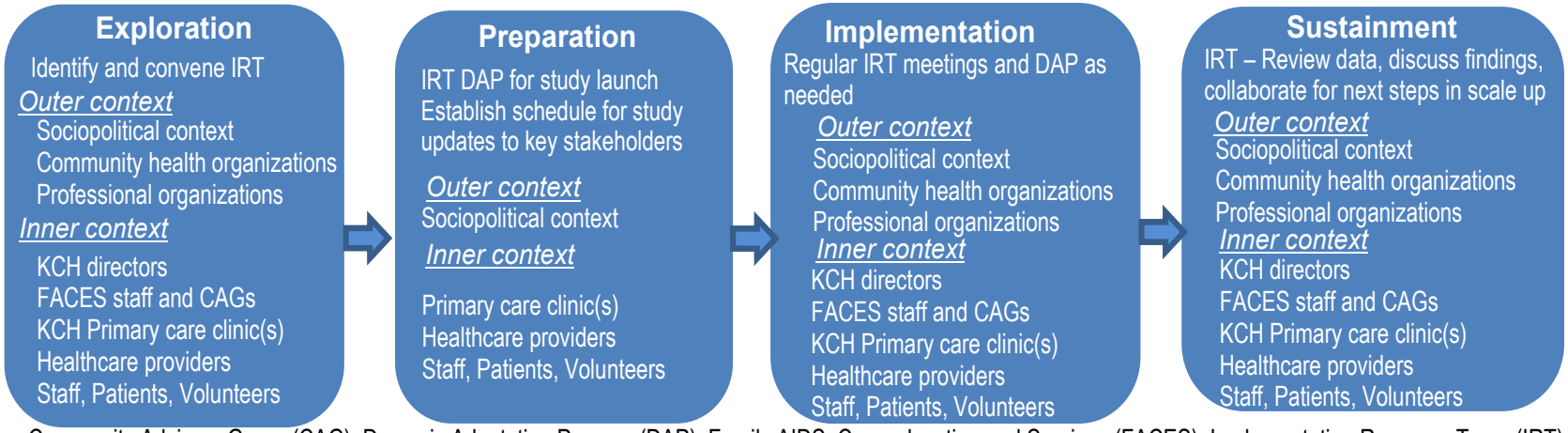
The in-depth interviews and focus group will be digitally recorded (sound, only), transcribed and translated so that we can study the in-depth interviews and focus group discussion and compile its findings with the other focus groups and interviews in this study. You will be assigned a study number and only the study number will be used in the audio-recording. Your name will not be used by the interviewer and participants will be asked not to refer to one another by name. After the focus group, the digital file will be uploaded on a computer to a secure server and the file will be erased from the recorder.

TIMELINE

Table 3: Research Timeline					
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Processing IRBs and sub-contracts					
EPIS model for collaborative implementation research with key stakeholders					
Aim 1: Hiring and training for SMART-DAPPER					
Aim 1: Recruitment to SMART-DAPPER through primary care clinic					
Aim 1: SMART-DAPPER, including follow-up					
Aim 2: Estimate the costs and cost-benefit ratios for fluoxetine and IPT treatment of depression.					
Data analysis					
Manuscript preparation					

Sequential, Multiple Assignment Randomized Trial (SMART) Depression And Primary care Partnership for Effectiveness-implementation Research (DAPPER); Exploration, Preparation, Implementation and Sustainment (EPIS); Internal Review Board (IRB); Interpersonal Psychotherapy (IPT).

Figure 2 - Exploration, Preparation, Implementation, Sustainment (EPIS) model



Community Advisory Group (CAG); Dynamic Adaptation Process (DAP); Family AIDS, Care education and Services (FACES); Implementation Resource Team (IRT); Kisumu County Hospital (KCH). **NOTE:** Adapted from Aarons et al (2011). Advancing a conceptual model of evidence-based practice implementation in public service sectors. Adm Policy Ment Health. 38: 4–2 (Figure 2).

Figure 3. SMART DAPPER Study Design

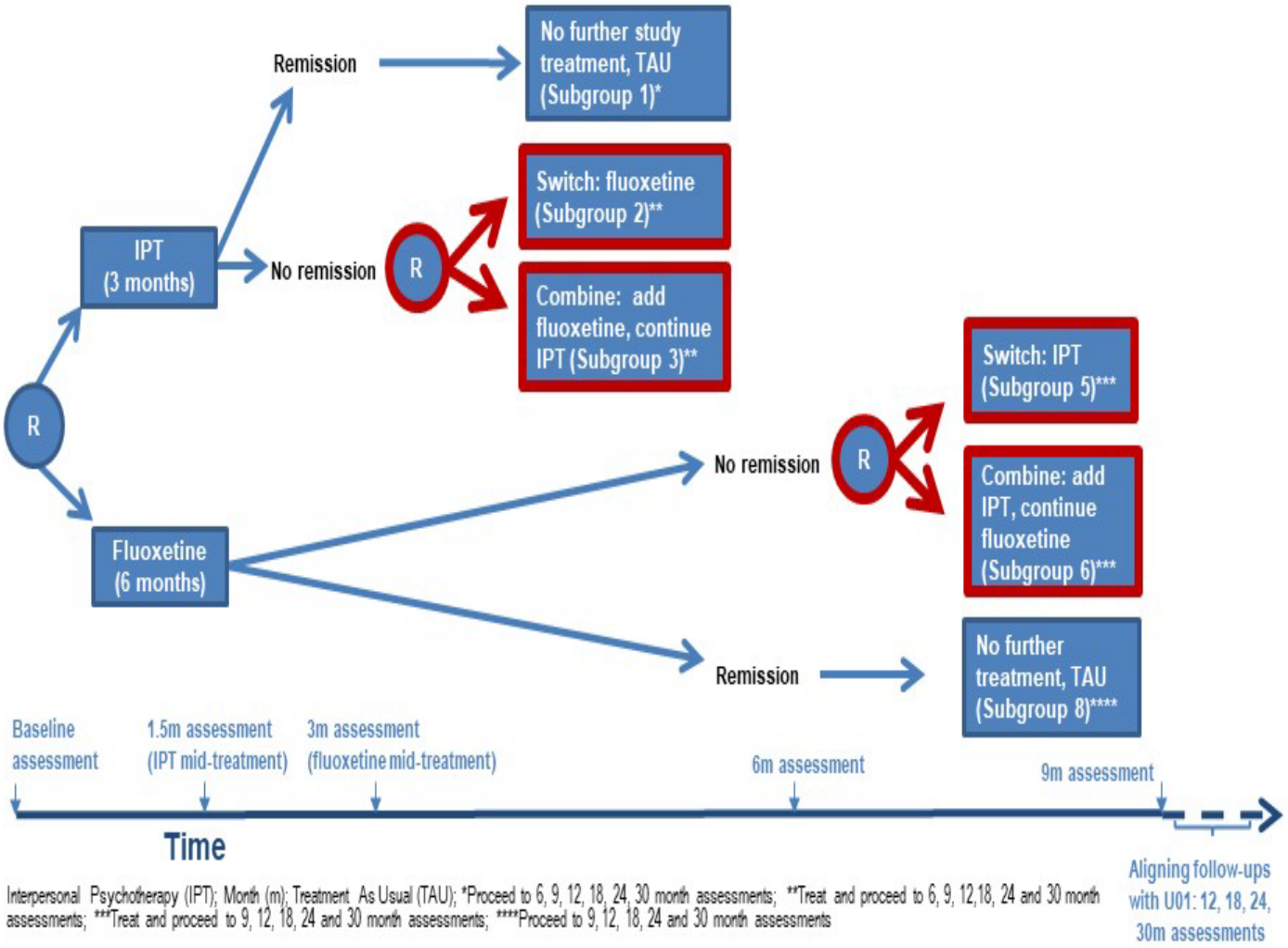
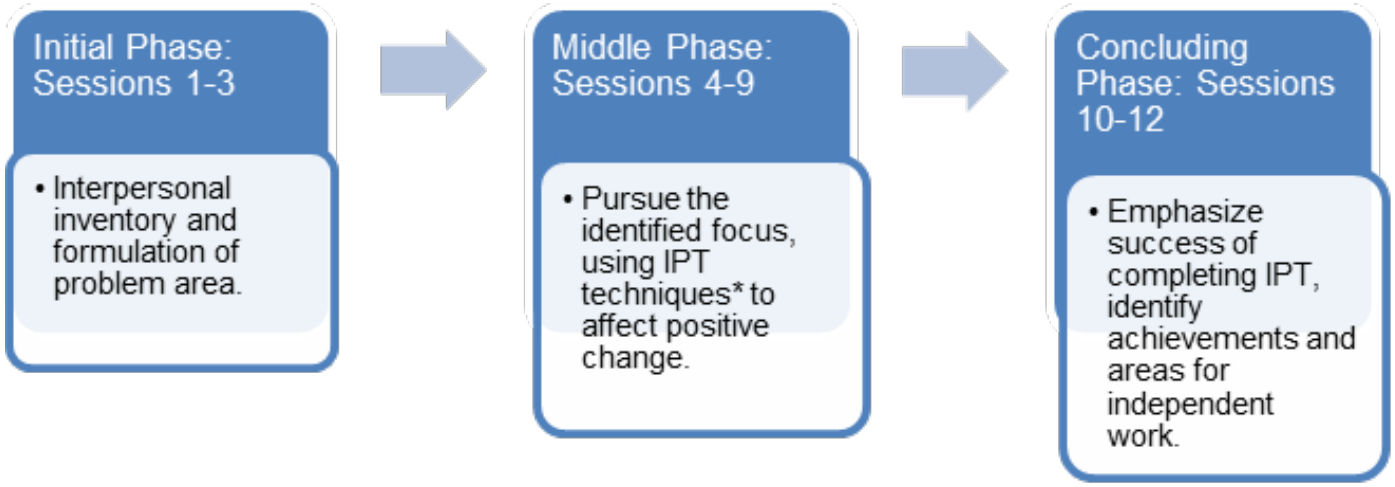


Figure 4: Interpersonal Psychotherapy Phases



REFERENCES

Aillon, J.-L., Ndetei, D. M., Khasakhala, L., Ngari, W. N., Achola, H. O., Akinyi, S., & Ribero, S. (2014). Prevalence, types and comorbidity of mental disorders in a Kenyan primary health centre. *Social Psychiatry and Psychiatric Epidemiology*, *49*(8), 1257–1268. https://doi.org/10.1007/s00127-013-0755-2

Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B., Monteiro, M. G., & World Health Organization. (2001). *AUDIT : the Alcohol Use Disorders Identification Test : guidelines for use in primary health care, 2nd ed*. Geneva: World Health Organization.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561–71.

Bhui, K., Mohamud, S., Warfa, N., Craig, T., & Stansfeld, S. A. (2003). Cultural adaptation of mental health measures: improving the quality of clinical practice and research. *The British Journal of Psychiatry*, *183*(3), 184–186. https://doi.org/10.1192/bjp.183.3.184

Bloom, D., Cafiero, E., Jane-llopis, E., Abrahams-Gessel, S., Bloom, L., Fathima, S., … Weinstein, C. (2011). *The Global Economic Burden of Non-communicable Diseases: World Economic Forum*. Geneva: World Economic Forum.

Bolton, P. (2001). Cross-cultural validity and reliability testing of a standard psychiatric assessment instrument without a gold standard. *The Journal of Nervous and Mental Disease*, *189*(4), 238–242.

Bradley MM, Lang PJ. Measuring emotion: The self-assessment manikin and the semantic differential. *Journal of Behavior Therapy and Experimental Psychiatry*. 1994;25(1):49-59.

Bukusi, D. (Ed.). (2015, August). Kenya Mental Health Policy 2015-2020: Towards Attaining the Highest Standard of Mental Health. Nairobi: Ministry of Health.

Cabassa, L. J., & Baumann, A. A. (2013). A two-way street: bridging implementation science and cultural adaptations of mental health treatments. *Implementation Science*, *8*, 90. https://doi.org/10.1186/1748-5908-8-90

Carlson, E. B., Smith, S. R., Palmieri, P. A., Dalenberg, C., Ruzek, J. I., Kimerling, R., … Spain, D. A. (2011). Development and validation of a brief self-report measure of trauma exposure: the Trauma History Screen. *Psychological Assessment*, *23*(2), 463–477. https://doi.org/10.1037/a0022294

Cattaneo, A., Macchi, F., Plazzotta, G., Veronica, B., Bocchio-Chiavetto, L., Riva, M. A., & Pariante, C. M. (2015). Inflammation and neuronal plasticity: a link between childhood trauma and depression pathogenesis. *Frontiers in Cellular Neuroscience*, *9*, 40. https://doi.org/10.3389/fncel.2015.00040

Chisholm, D., Heslin, M., Docrat, S., Nanda, S., Shidhaye, R., Upadhaya, N., … Lund, C.

(2016). Scaling-up services for psychosis, depression and epilepsy in sub-Saharan Africa and South Asia: development and application of a mental health systems planning tool (OneHealth). *Epidemiology and Psychiatric Sciences*, 1–11. https://doi.org/10.1017/S2045796016000408

Curran, G. M., Bauer, M., Mittman, B., Pyne, J. M., & Stetler, C. (2012). Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Medical Care*, *50*(3), 217–26. https://doi.org/10.1097/MLR.0b013e3182408812

D V Sheehan, Y. L. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59 Suppl 2*, 22-33-57.

de Jong, J. T. V. M., & van Ommeren, M. (2002). Toward a Culture-Informed Epidemiology: Combining Qualitative and Quantitative Research in Transcultural Contexts. *Transcultural Psychiatry*, *39*(4), 422–433. https://doi.org/10.1177/136346150203900402

DeRubeis, R. J., Siegle, G. J., & Hollon, S. D. (2008). Cognitive therapy vs. medications for depression: Treatment outcomes and neural mechanisms. *Nature Reviews. Neuroscience*, *9*(10), 788–796. https://doi.org/10.1038/nrn2345

Farris, R. P., Will, J. C., Khavjou, O., & Finkelstein, E. A. (2007). Beyond effectiveness: evaluating the public health impact of the WISEWOMAN program. *American Journal of Public Health*, *97*(4), 641–647. https://doi.org/10.2105/AJPH.2005.072264

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J. L., … Whiteford, H. A. (2013). Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLOS Med*, *10*(11), e1001547. https://doi.org/10.1371/journal.pmed.1001547

Gartlehner, G., Gaynes, B. N., Amick, H. R., Asher, G., Morgan, L. C., Coker-Schwimmer, E., … Lohr, K. N. (2015). *Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder*. Rockville (MD): Agency for Healthcare Research and Quality (US).

Gelenberg, A. J., Freeman, M., Markowitz, J. C., Rosenbaum, J. F., Michael, T., Trivedi, M. H., & van Rhoads, R. S. (2010, October). Practice Guideline for the Treatment of Patients With Major Depressive Disorder.

Gilbody, S., Bower, P., Fletcher, J., Richards, D., & Sutton, A. J. (2006). Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Archives of Internal Medicine*, *166*(21), 2314–2321. https://doi.org/10.1001/archinte.166.21.2314

Glasgow, R. E., Klesges, L. M., Dzewaltowski, D. A., Estabrooks, P. A., & Vogt, T. M.

(2006). Evaluating the impact of health promotion programs: using the RE-AIM framework to form summary measures for decision making involving complex issues. *Health Education Research*, *21*(5), 688–694. https://doi.org/10.1093/her/cyl081

Glasgow, R. E., Vogt, T. M., & Boles, S. M. (1999). Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *American Journal of Public Health*, *89*(9), 1322–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10474547

Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. (2015). *The Lancet*, *386*(9995), 743–800. https://doi.org/10.1016/S0140-6736(15)60692-4

Hanlon, C., Luitel, N. P., Kathree, T., Murhar, V., Shrivasta, S., Medhin, G., … Prince, M. (2014). Challenges and Opportunities for Implementing Integrated Mental Health Care: A District Level Situation Analysis from Five Low- and Middle-Income Countries. *PLoS ONE*, *9*(2), e88437. https://doi.org/10.1371/journal.pone.0088437

HANLON, C., WONDIMAGEGN, D., & ALEM, A. (2010). Lessons learned in developing community mental health care in Africa. *World Psychiatry*, *9*(3), 185–189.

Haviland, A. M., & Nagin, D. S. (2005). Causal inferences with group based trajectory models. *Psychometrika*, *70*(3), 557–578. https://doi.org/10.1007/s11336-004-1261-y

Hirschfeld R, Williams J, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. Am J Psychiatry. 2000;157:1873-1875

Hien, D. A., Levin, F. R., Ruglass, L. M., López-Castro, T., Papini, S., Hu, M.-C., … Herron, A. (2015). Combining seeking safety with sertraline for PTSD and alcohol use disorders: A randomized controlled trial. *Journal of Consulting and Clinical Psychology*, *83*(2), 359–369. https://doi.org/10.1037/a0038719

Horowitz, L. M., Snyder, D. J., Boudreaux, E. D., He, J. P., Harrington, C. J., Cai, J., Claassen, C. A., Salhany, J. E., Dao, T., Chaves, J. F., Jobes, D. A., Merikangas, K. R., Bridge, J. A., Pao, M. (2020). Validation of the Ask Suicide-Screening Questions (ASQ) for adult medical inpatients: A brief tool for all ages. *Psychosomatics, 61*(6), 713-722.

Hyman, S. E. (2014). The unconscionable gap between what we know and what we do. *Science Translational Medicine*, *6*(253), 253cm9. https://doi.org/10.1126/scitranslmed.3010312

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., … Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework

for research on mental disorders. *The American Journal of Psychiatry*, *167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

Jacob, V., Chattopadhyay, S. K., Sipe, T. A., Thota, A. B., Byard, G. J., & Chapman, D. P. (2012). Economics of collaborative care for management of depressive disorders: a community guide systematic review. *American Journal of Preventive Medicine*, *42*(5), 539–549. https://doi.org/10.1016/j.amepre.2012.01.011

Jakubovski, E., Varigonda, A. L., Freemantle, N., Taylor, M. J., & Bloch, M. H. (2016). Systematic Review and Meta-Analysis: Dose-Response Relationship of Selective Serotonin Reuptake Inhibitors in Major Depressive Disorder. *American Journal of Psychiatry*, *173*(2), 174–183. https://doi.org/10.1176/appi.ajp.2015.15030331

Jamison, D. T., Summers, L. H., Alleyne, G., Arrow, K. J., Berkley, S., Binagwaho, A., … Yamey, G. (2013). Global health 2035: a world converging within a generation. *Lancet (London, England)*, *382*(9908), 1898–1955. https://doi.org/10.1016/S0140-6736(13)62105-4

Jenkins, R., Othieno, C., Okeyo, S., Aruwa, J., Wallcraft, J., & Jenkins, B. (2013). Exploring the perspectives and experiences of health workers at primary health facilities in Kenya following training. *International Journal of Mental Health Systems*, *7*(1), 6. https://doi.org/10.1186/1752-4458-7-6

Jenkins, R., Othieno, C., Okeyo, S., Kaseje, D., Aruwa, J., Oyugi, H., … Kauye, F. (2013). Short structured general mental health in service training programme in Kenya improves patient health and social outcomes but not detection of mental health problems - a pragmatic cluster randomised controlled trial. *International Journal of Mental Health Systems*, *7*(1), 25. https://doi.org/10.1186/1752-4458-7-25

Jenkins, R., Othieno, C., Ongeri, L., Ogutu, B., Sifuna, P., Kingora, J., … Omollo, R. (2015). Adult psychotic symptoms, their associated risk factors and changes in prevalence in men and women over a decade in a poor rural district of Kenya. *International Journal of Environmental Research and Public Health*, *12*(5), 5310–5328. https://doi.org/10.3390/ijerph120505310

Jenkins, R., Othieno, C., Ongeri, L., Sifuna, P., Ongecha, M., Kingora, J., … Ogutu, B. (2015). Common mental disorder in Nyanza province, Kenya in 2013 and its associated risk factors--an assessment of change since 2004, using a repeat household survey in a demographic surveillance site. *BMC Psychiatry*, *15*(1), 309. https://doi.org/10.1186/s12888-015-0693-5

Jiang, R. F., Tong, H., Delucchi, K. L., Neylan, T. C., Shi, Q., & Meffert, S. M. (2014). Interpersonal psychotherapy versus treatment as usual for PTSD and depression among Sichuan earthquake survivors: a randomized clinical trial. *Conflict and Health*, *8*(1), 14. https://doi.org/10.1186/1752-1505-8-14

Kassebaum, N. J., Arora, M., Barber, R. M., Bhutta, Z. A., Brown, J., Carter, A., … Murray, C. J. L. (2016). Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–

2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, *388*(10053), 1603–1658. https://doi.org/10.1016/S0140-6736(16)31460-X

Katon, W. J. (2003). Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biological Psychiatry*, *54*(3), 216–226.

Khanassov, V., Pluye, P., Descoteaux, S., Haggerty, J. L., Russell, G., Gunn, J., & Levesque, J.-F. (2016). Organizational interventions improving access to community-based primary health care for vulnerable populations: a scoping review. *International Journal for Equity in Health*, *15*. https://doi.org/10.1186/s12939-016-0459-9

Kroenke K, Spitzer RL, Williams JBW. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care*. 2003;41(11):1284-1292.

Kiima, D. (2015, May). Personal Communication with Dr. David Kiima, Country Director of Mental Health, Kenya.

Lee, D. J., Schnitzlein, C. W., Wolf, J. P., Vythilingam, M., Rasmusson, A. M., & Hoge, C. W. (2016). Psychotherapy versus Pharmacotherapy for Posttraumatic Stress Disorder: Systemic Review and Meta-Analyses to Determine First-Line Treatments. *Depression and Anxiety*. https://doi.org/10.1002/da.22511

Levesque, J.-F., Harris, M. F., & Russell, G. (2013). Patient-centred access to health care: conceptualising access at the interface of health systems and populations. *International Journal for Equity in Health*, *12*, 18. https://doi.org/10.1186/1475-9276-12-18

Lund, C., De Silva, M., Plagerson, S., Cooper, S., Chisholm, D., Das, J., … Patel, V. (2011). Poverty and mental disorders: breaking the cycle in low-income and middle-income countries. *The Lancet*, *378*(9801), 1502–1514. https://doi.org/10.1016/S0140-6736(11)60754-X

Meffert, S. M., Neylan, T. C., Chambers, D. A., & Verdeli, H. (2016). Novel implementation research designs for scaling up global mental health care: overcoming translational challenges to address the world's leading cause of disability. *International Journal of Mental Health Systems*, *10*, 19. https://doi.org/10.1186/s13033-016-0049-7

Meffert, S. M., Neylan, T. C., Ongeri, L., Rota, G., Onu, C., & Verdeli, H. (n.d.). Novel Implementation Research Designs for Scaling up Global Mental Health Care: Overcoming Translational Challenges to Address the World's Leading Cause of Disability. *Internation Journal of Mental Health Systems*.

Mugisha, J., Abdulmalik, J., Hanlon, C., Petersen, I., Lund, C., Upadhaya, N., … Kigozi, F. (2017). Health systems context(s) for integrating mental health into primary health care in six Emerald countries: a situation analysis. *International Journal of Mental Health Systems*, *11*, 7. https://doi.org/10.1186/s13033-016-0114-2

Murray, C. J. L., Barber, R. M., Foreman, K. J., Ozgoren, A. A., Abd-Allah, F., Abera, S. F., … Vos, T. (2015). Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. *The Lancet*, *386*(10009), 2145–2191. https://doi.org/10.1016/S0140-6736(15)61340-X

Murray, C. J. L., & Lopez, A. D. (1996). *The Global Burden of Disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Cambridge: Harvard University Press.

Ndetei, D. M., Khasakhala, L. I., Kuria, M. W., Mutiso, V. N., Ongecha-Owuor, F. A., & Kokonya, D. A. (2009). The prevalence of mental disorders in adults in different level general medical facilities in Kenya: a cross-sectional study. *Annals of General Psychiatry*, *8*, 1. https://doi.org/10.1186/1744-859X-8-1

NIMH » Major Depression Among Adults. (n.d.).

Palsson, O., Ballou, S., The U.S. National Pandemic Emotional Impact Scale, Findings of a nationwide survey assessing the effects of the COVID-19 pandemic on the emotional wellbeing of the U.S. adult population. 2020

Obrist, B., Iteba, N., Lengeler, C., Makemba, A., Mshana, C., Nathan, R., … Mshinda, H. (2007). Access to Health Care in Contexts of Livelihood Insecurity: A Framework for Analysis and Action. *PLOS Medicine*, *4*(10), e308. https://doi.org/10.1371/journal.pmed.0040308

Ongeri, L., McCulloch, C. E., Neylan, T. C., Bukusi, E. A., Macfarlane, S., Othieno, C. J., … Meffert, S. M. (n.d.). Preliminary Findings: Prevalence of Mental Disorders among outpatients at Kaloleni district hospital, Kenya.Preliminary Findings: Prevalen.

Onu, C., Ongeri, L., Bukusi, E., Cohen, C. R., Neylan, T. C., Oyaro, P., … Meffert, S. M. (2016). Interpersonal psychotherapy for depression and posttraumatic stress disorder among HIV-positive women in Kisumu, Kenya: study protocol for a randomized controlled trial. *Trials*, *17*(1), 64. https://doi.org/10.1186/s13063-016-1187-6

Onu, C., Ongeri, L., Rota, G., Atewa, F., & Meffert, S. M. (n.d.). Mental health hIv aNd Domestic violence (MIND) T2 Protocol: Treating Depression and Posttraumatic Stress Disorder (PTSD) among HIV-positive women affected by Gender Based Violence -- A Randomized Controlled Trial of Interpersonal Psychotherapy integrated . *In Submission*.

Organization, W. H. (2008). No Title.

Patel, V., Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., … Bolton, P. (2016). From delivery science to discovery science: realising the full potential of global mental health. *Epidemiology and Psychiatric Sciences*, *501*(7465), 1–4. https://doi.org/10.1017/S2045796016000263

Patel, V., Chisholm, D., Parikh, R., Charlson, F. J., Degenhardt, L., Dua, T., … DCP MNS Author Group. (2016). Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. *Lancet (London, England)*, *387*(10028), 1672–85. https://doi.org/10.1016/S0140-6736(15)00390-6

Patel, V., Minas, H., Cohen, A., Prince, M., Fisher, J., Herrman, H., … Chandra, P. S. (2013). Global Mental Health: Principles and Practice. https://doi.org/10.1093/med/9780199920181.003.0016

Penchansky, R., & Thomas, J. W. (1981). The concept of access: definition and relationship to consumer satisfaction. *Medical Care*, *19*(2), 127–140.

Prins, A., Bovin, M. J., Kimerling, R., Kaloupek, D. G., Marx, B. P., Pless Kaiser, A., & Schnurr, P. P. (2015). *The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)*

Raftery, A. E. (1995). Bayesian Model Selection in Social Research. *Sociological Methodology*, *25*, 111. https://doi.org/10.2307/271063

Roca, M., Gili, M., Garcia-Garcia, M., Salva, J., Vives, M., Garcia Campayo, J., & Comas, A. (2009). Prevalence and comorbidity of common mental disorders in primary care. *Journal of Affective Disorders*, *119*(1–3), 52–58. https://doi.org/10.1016/j.jad.2009.03.014

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., … Fava, M. (2006). Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report. *American Journal of Psychiatry*, *163*(11), 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Schneier, F. R., Neria, Y., Pavlicova, M., Hembree, E., Suh, E. J., Amsel, L., & Marshall, R. D. (2012). Combined prolonged exposure therapy and paroxetine for PTSD related to the World Trade Center attack: a randomized controlled trial. *The American Journal of Psychiatry*, *169*(1), 80–88. https://doi.org/10.1176/appi.ajp.2011.11020321

Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 Suppl 20:22-33;quiz 34-57.

Shidhaye, R., Lund, C., & Chisholm, D. (2015). Closing the treatment gap for mental, neurological and substance use disorders by strengthening existing health care platforms: strategies for delivery and integration of evidence-based interventions. *International Journal of Mental Health Systems*, *9*, 40. https://doi.org/10.1186/s13033-015-0031-9

Skinner, H. (1982). The Drug Abuse Screening Test. *Addictive Behavior*, *7*(4), 363–371.

Smit, J., van den Berg, C. E., Bekker, L.-G., Seedat, S., & Stein, D. J. (2006). Translation and cross-cultural adaptation of a mental health battery in an African setting. *African Health Sciences*, *6*(4), 215–22. https://doi.org/10.5555/afhs.2006.6.4.215

Sousa, V. D., & Rojjanasrirat, W. (2011). Translation, adaptation and validation of instruments or scales for use in cross-cultural health care research: a clear and user-friendly guideline. *Journal of Evaluation in Clinical Practice*, *17*(2), 268–274. https://doi.org/10.1111/j.1365-2753.2010.01434.x

Spielmans, G. I., Berman, M. I., & Usitalo, A. N. (2011). Psychotherapy Versus Second-Generation Antidepressants in the Treatment of Depression. *The Journal of Nervous and Mental Disease*, *199*(3), 142–149. https://doi.org/10.1097/NMD.0b013e31820caefb

STRAUS, M. A., HAMBY, S. L., BONEY-McCOY, S., & SUGARMAN, D. B. (1996). The Revised Conflict Tactics Scales (CTS2): Development and Preliminary Psychometric Data. *Journal of Family Issues*, *17*(3), 283–316. https://doi.org/10.1177/019251396017003001

Thornicroft, G., Chatterji, S., Evans-Lacko, S., Gruber, M., Sampson, N., Aguilar-Gaxiola, S., … Kessler, R. C. (2016). Undertreatment of people with major depressive disorder in 21 countries. *The British Journal of Psychiatry*, bjp.bp.116.188078. https://doi.org/10.1192/bjp.bp.116.188078

Thota, A. B., Sipe, T. A., Byard, G. J., Zometa, C. S., Hahn, R. A., McKnight-Eily, L. R., … Williams, S. P. (2012). Collaborative care to improve the management of depressive disorders: a community guide systematic review and meta-analysis. *American Journal of Preventive Medicine*, *42*(5), 525–538. https://doi.org/10.1016/j.amepre.2012.01.019

Üstün, T. B., Chatterji, S., Kostanjsek, N., Rehm, J., Kennedy, C., Epping-Jordan, J., … Pull, C. (2010). Developing the World Health Organization Disability Assessment Schedule 2.0. *Bulletin of the World Health Organization*, *88*(11), 815–823. https://doi.org/10.2471/BLT.09.067231

van Ginneken, N., Tharyan, P., Lewin, S., Rao, G. N., Meera, S., Pian, J., … Patel, V. (2013). Non-specialist health worker interventions for the care of mental, neurological and substance-abuse disorders in low- and middle-income countries. *The Cochrane Database of Systematic Reviews*, *11*, CD009149. https://doi.org/10.1002/14651858.CD009149.pub2

Verdeli, H., Clougherty, K., Bolton, P., Speelman, L., Lincoln, N., Bass, J., … Weissman, M. M. (2003). Adapting group interpersonal psychotherapy for a developing country: experience in rural Uganda. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *2*(2), 114–20.

Wagner, G. J., Ngo, V., Akena, D., & Seggane, M. (2014, January). Integration of Depression Treatment in HIV Care: A Manual for Depression Care in HIV.

Wagner, G. J., Ngo, V., Glick, P., Obuku, E. A., Musisi, S., & Akena, D. (2014). INtegration of DEPression Treatment into HIV Care in Uganda (INDEPTH-Uganda): study protocol for a randomized controlled trial. *Trials*, *15*(1), 248. https://doi.org/10.1186/1745-6215-15-248

Whiteford, H. A., Harris, M. G., McKeon, G., Baxter, A., Pennell, C., Barendregt, J. J., & Wang, J. (2013). Estimating remission from untreated major depression: a systematic review and meta-analysis. *Psychological Medicine*, *43*(8), 1569–1585. https://doi.org/10.1017/S0033291712001717

WHO | Framework on Integrated People-Centred Health Services. (n.d.).

Zimet GD, Dahlem N, Zimet S, Farley GK. The multidimensional scale of perceived social support. *Journal of Personality Assessment*. 1988;52:30-41.

Zunner, B., Dworkin, S. L., Neylan, T. C., Bukusi, E. A., Oyaro, P., Cohen, C. R., … Meffert, S. M. (2015). HIV, violence and women: Unmet mental health care needs. *Journal of Affective Disorders*, *174*, 619–626. https://doi.org/10.1016/j.jad.2014.12.017